# Human Secreted Proteins

# Related Applications

[0001] This application is a continuation-in-part of PCT/US02/08124, filed March 19, 2002, which in turn claims benefit of the following:

| Application::  | Continuity Type::       | Parent Application:: | Parent Filing<br>Date:: |
|----------------|-------------------------|----------------------|-------------------------|
| PCT/US02/08124 | Continuation-in-part of | 10/100,683           | 03/19/02                |
| 10/100,683     | Non-provisional of      | 60/277,340           | 03/21/01                |
| 10/100,683     | Non-provisional of      | 60/306,171           | 07/19/01                |
| 10/100,683     | Non-provisional of      | 60/331,287           | 11/13/01                |
| 10/100,683     | Continuation-in-part of | 09/981,876           | 10/19/01                |
| 09/981,876     | Divisional of           | 09/621,011           | 07/20/00                |
| 09/621,011     | Continuation of         | 09/148,545           | 09/04/98                |
| 09/148,545     | Continuation-in-part of | PCT/US98/04482       | 03/06/98                |
| 10/100,683     | Continuation-in-part of | 09/621,011           | 07/20/00                |
| 09/621,011     | Continuation of         | 09/148,545           | 09/04/98                |
| 09/148,545     | Continuation-in-part of | PCT/US98/04482       | 03/06/98                |
| 10/100,683     | Continuation-in-part of | 09/148,545           | 09/04/98                |
| 09/148,545     | Continuation-in-part of | PCT/US98/04482       | 03/06/98                |
| 10/100,683     | Continuation-in-part of | PCT/US98/04482       | 03/06/98                |
| PCT/US98/04482 | Non-provisional of      | 60/040,162           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/040,333           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/038,621           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/040,161           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/040,626           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/040,334           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/040,336           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/040,163           | 03/07/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,615           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,600           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,597           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,502           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,633           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,583           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,617           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,618           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,503           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,592           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,581           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,584           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,500           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,587           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,492           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,598           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,613           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,582           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047.596           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,612           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,632           | 05/23/97                |
| PCT/US98/04482 | Non-provisional of      | 60/047,601           | 05/23/97                |

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|----------------------------------|------------------------------------------|------------|----------------------|
| PCT/US98/04482                   | Non-provisional of                       | 60/043,580 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,568 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,314 | 04/11/97             |
| PCT/US98/04482<br>PCT/US98/04482 | Non-provisional of                       | 60/043,569 | 04/11/97<br>04/11/97 |
|                                  | Non-provisional of                       |            |                      |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,671 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,674 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,669 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,312 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,313 | 04/11/97             |
| PCT/US98/04482<br>PCT/US98/04482 | Non-provisional of<br>Non-provisional of | 60/043,672 | 04/11/97<br>04/11/97 |
|                                  |                                          | 60/043,315 |                      |
| PCT/US98/04482                   | Non-provisional of                       | 60/048,974 | 06/06/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,886 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,877 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,889 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,893 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,630 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,878 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,662 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,872 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,882 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,637 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,903 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,888 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,879 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,880 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,894 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,911 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,636 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,874 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,910 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,864 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,631 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,845 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,892 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,595 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/057,761 | 09/05/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,599 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,588 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,585 | 05/23/97             |
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| PCT/US98/04482                   | Non-provisional of                       | 60/047,594 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,589 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,593 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,614 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,578 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,576 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/047,501 | 05/23/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/043,670 | 04/11/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,632 | 08/22/97             |
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| PCT/US98/04482                   | Non-provisional of                       | 60/056,881 | 08/22/97             |
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| PCT/US98/04482                   | Non-provisional of                       | 60/056,875 | 08/22/97             |
| PCT/US98/04482                   | Non-provisional of                       | 60/056,862 | 08/22/97             |

| PCT/US98/04482 | Non-provisional of      | 60/056,887     | 08/22/97 |
|----------------|-------------------------|----------------|----------|
| PCT/US98/04482 | Non-provisional of      | 60/056,908     | 08/22/97 |
| PCT/US98/04482 | Non-provisional of      | 60/048,964     | 06/06/97 |
| PCT/US98/04482 | Non-provisional of      | 60/057,650     | 09/05/97 |
| PCT/US98/04482 | Non-provisional of      | 60/056,884     | 08/22/97 |
| 10/100,683     | Continuation-in-part of | 09/882,171     | 06/18/01 |
| 09/882,171     | Non-provisional of      | 60/190,068     | 03/17/00 |
| 09/882,171     | Continuation of         | 09/809.391     | 03/16/01 |
| 09/809,391     | Continuation-in-part of | 09/149,476     | 09/08/98 |
| 09/149,476     | Continuation-in-part of | PCT/US98/04493 | 03/06/98 |
| 10/100,683     | Continuation-in-part of | 09/809.391     | 03/16/01 |
| 09/809,391     | Non-provisional of      | 60/190.068     | 03/17/00 |
| 09/809,391     | Continuation-in-part of | 09/149,476     | 09/08/98 |
| 09/149,476     | Continuation-in-part of | PCT/US98/04493 | 03/06/98 |
| 10/100,683     | Continuation-in-part of | 09/149,476     | 09/08/98 |
| 09/149,476     | Continuation-in-part of | PCT/US98/04493 | 03/06/98 |
| 10/100,683     | Continuation-in-part of | PCT/US98/04493 | 03/06/98 |
| PCT/US98/04493 | Non-provisional of      | 60/040,161     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/040,162     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/040,333     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/038,621     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/040,626     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/040,334     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/040,336     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/040,163     | 03/07/97 |
| PCT/US98/04493 | Non-provisional of      | 60/047,600     | 05/23/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/047,597     | 05/23/97 |
| PCT/US98/04493 | Non-provisional of      | 60/047,502     | 05/23/97 |
| PCT/US98/04493 | Non-provisional of      | 60/047,633     | 05/23/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/047,617     | 05/23/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/047,581     | 05/23/97 |
| PCT/US98/04493 | Non-provisional of      | 60/047,584     | 05/23/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/047,598     | 05/23/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/047,596     | 05/23/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/047,601     | 05/23/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,580     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,568     | 04/11/97 |
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| PCT/US98/04493 | Non-provisional of      | 60/043,569     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,311     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,671     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,674     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,669     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,312     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,313     | 04/11/97 |
| PCT/US98/04493 | Non-provisional of      | 60/043,672     | 04/11/97 |

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|----------------------------------|------------------------------------------|--------------------------|----------------------|
| PCT/US98/04493                   | Non-provisional of                       | 60/043,315               | 04/11/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/048,974               | 06/06/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,886               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,877               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,889               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,893               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,630               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,878               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,662               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,872               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,882               | 08/22/97             |
| PCT/US98/04493<br>PCT/US98/04493 | Non-provisional of                       | 60/056,637               | 08/22/97<br>08/22/97 |
|                                  | Non-provisional of                       |                          |                      |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,888               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,879               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,880               | 08/22/97             |
| PCT/US98/04493<br>PCT/US98/04493 | Non-provisional of                       | 60/056,894               | 08/22/97<br>08/22/97 |
|                                  | Non-provisional of                       | 60/056,911               |                      |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,636               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,874               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,910               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,864               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,631               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,845               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,892               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/057,761               | 09/05/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/047,595               | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/047,599               | 05/23/97             |
| PCT/US98/04493<br>PCT/US98/04493 | Non-provisional of                       | 60/047,588<br>60/047,585 | 05/23/97<br>05/23/97 |
| PCT/US98/04493<br>PCT/US98/04493 | Non-provisional of                       |                          | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of<br>Non-provisional of | 60/047,586<br>60/047,590 | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/047,590               | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/047,594               | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/047,589               | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/047,593               | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/043,578               | 04/11/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/043,576               | 04/11/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/043,576               | 05/23/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/043,670               | 04/11/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,632               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,664               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,876               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,881               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,881               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,875               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,862               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,887               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,908               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/048,964               | 06/06/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/057,650               | 09/05/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/056,884               | 08/22/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/057,669               | 09/05/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/049,610               | 06/13/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/049,610               | 10/02/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/051,926               | 07/08/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/051,926               | 07/16/97             |
| PCT/US98/04493                   | Non-provisional of                       | 60/052,874               | 09/12/97             |
| FC1/US98/04493                   | inon-provisional of                      | 00/038,783               | 09/12/97             |

| PCT/US98/04493                   | Non-provisional of      | 60/055,724               | 08/18/97 |
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| 10/100,683                       | Continuation-in-part of | 10/058,993               | 01/30/02 |
| 10/058,993                       | Non-provisional of      | 60/265,583               | 02/02/01 |
| 10/058,993                       | Continuation-in-part of | 09/852,659               | 05/11/01 |
| 09/852,659                       | Continuation-in-part of | 09/152,060               | 09/11/98 |
| 09/152,060                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/058,993                       | Continuation-in-part of | 09/853,161               | 05/11/01 |
| 09/853,161                       | Continuation-in-part of | 09/152,060               | 09/11/98 |
| 09/152,060                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/058,993                       | Continuation-in-part of | 09/852,797               | 05/11/01 |
| 09/852,797                       | Continuation-in-part of | 09/152,060               | 09/11/01 |
| 09/852,797                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/100,683                       | Continuation-in-part of | 09/852,659               | 05/11/01 |
|                                  | Non-provisional of      |                          |          |
| 09/852,659                       |                         | 60/265,583               | 02/02/01 |
| 09/852,659                       | Continuation-in-part of | 09/152,060               | 09/11/98 |
| 09/152,060                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/100,683                       | Continuation-in-part of | 09/853,161               | 05/11/01 |
| 09/853,161                       | Non-provisional of      | 60/265,583               | 02/02/01 |
| 09/853,161                       | Continuation-in-part of | 09/152,060               | 09/11/98 |
| 09/152,060                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/100,683                       | Continuation-in-part of | 09/852,797               | 05/11/01 |
| 09/852,797                       | Non-provisional of      | 60/265,583               | 02/02/01 |
| 09/852,797                       | Continuation-in-part of | 09/152,060               | 09/11/98 |
| 09/152,060                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/100,683                       | Continuation-in-part of | 09/152,060               | 09/11/98 |
| 09/152,060                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| 10/100,683                       | Continuation-in-part of | PCT/US98/04858           | 03/12/98 |
| PCT/US98/04858                   | Non-provisional of      | 60/040,762               | 03/14/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/040,710               | 03/14/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/050,934               | 05/30/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/048,100               | 05/30/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/048,357               | 05/30/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/048,189               | 05/30/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/057,765               | 09/05/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/048,970               | 06/06/97 |
| PCT/US98/04858                   | Non-provisional of      | 60/068,368               | 12/19/97 |
| 10/100,683                       | Continuation-in-part of | 10/059,395               | 01/31/02 |
| 10/059,395                       | Divisional of           | 09/966,262               | 10/01/01 |
| 09/966,262                       | Continuation of         | 09/154.707               | 09/17/98 |
| 09/154,707                       | Continuation-in-part of | PCT/US98/05311           | 03/19/98 |
| 10/100,683                       | Continuation-in-part of | 09/984,245               | 10/29/01 |
| 09/984,245                       | Divisional of           | 09/154,707               | 09/17/98 |
| 09/984,245                       | Continuation-in-part of | PCT/US98/05311           | 03/19/98 |
|                                  |                         |                          |          |
| 10/100,683                       | Continuation-in-part of | 09/983,966               | 10/26/01 |
| 09/983,966                       | Divisional of           | 09/154,707               | 09/17/98 |
| 09/154,707                       | Continuation-in-part of | PCT/US98/05311           | 03/19/98 |
| 10/100,683                       | Continuation-in-part of | 09/966,262               | 10/01/01 |
| 09/966,262                       | Continuation of of      | 09/154,707               | 09/17/98 |
| 09/154,707                       | Continuation-in-part of | PCT/US98/05311           | 03/19/98 |
| 10/100,683                       | Continuation-in-part of | 09/154,707               | 09/17/98 |
| 09/154,707                       | Continuation-in-part of | PCT/US98/05311           | 03/19/98 |
| 10/100,683                       | Continuation-in-part of | PCT/US98/05311           | 03/03/98 |
| PCT/US98/05311                   | Non-provisional of      | 60/041,277               | 03/21/97 |
| PCT/US98/05311                   | Non-provisional of      | 60/042,344               | 03/21/97 |
|                                  |                         |                          |          |
| PCT/US98/05311                   | Non-provisional of      | 60/041,276               | 03/21/97 |
| PCT/US98/05311<br>PCT/US98/05311 |                         | 60/041,276<br>60/041,281 | 03/21/97 |
|                                  | Non-provisional of      |                          |          |

| PCT/US98/05311                   | N                                        | 60/048.188     | 05/30/97 |
|----------------------------------|------------------------------------------|----------------|----------|
| PCT/US98/05311                   | Non-provisional of                       | 60/048,188     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of<br>Non-provisional of | 60/050,937     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/030,937     | 05/30/97 |
| PCT/US98/05311                   |                                          | 60/048,099     | 05/30/97 |
|                                  | Non-provisional of                       | 60/048,352     |          |
| PCT/US98/05311<br>PCT/US98/05311 | Non-provisional of<br>Non-provisional of | 60/048,352     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,186     | 05/30/97 |
| PCT/US98/05311                   |                                          |                |          |
|                                  | Non-provisional of                       | 60/048,095     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,131     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,096     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,355     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,160     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,351     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/048,154     | 05/30/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/054,804     | 08/05/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/056,370     | 08/19/97 |
| PCT/US98/05311                   | Non-provisional of                       | 60/060,862     | 10/02/97 |
| 10/100,683                       | Continuation-in-part of                  | 09/814,122     | 00.00.00 |
| 00/01/120                        |                                          | 00/555 145     | 03/22/01 |
| 09/814,122                       | Continuation of                          | 09/577,145     | 05/24/00 |
| 09/577,145                       | Continuation of                          | 09/166,780     | 10/06/98 |
| 09/166,780                       | Continuation-in-part of                  | PCT/US98/06801 | 04/07/98 |
| 10/100,683                       | Continuation-in-part of                  | PCT/US98/06801 | 04/07/98 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,726     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,727     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,728     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,754     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,825     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/048,068     | 05/30/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/048,070     | 05/30/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/048,184     | 05/30/97 |
| 10/100,683                       | Continuation-in-part of                  | PCT/US98/06801 | 04/07/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,726     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,727     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,728     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,754     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/042,825     | 04/08/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/048,068     | 05/30/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/048,070     | 05/30/97 |
| PCT/US98/06801                   | Non-provisional of                       | 60/048,184     | 05/30/97 |
| 10/100,683                       | Continuation-in-part of                  | PCT/US98/10868 | 05/28/98 |
| PCT/US98/10868                   | Non-provisional of                       | 60/044,039     | 05/30/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/048,093     | 05/30/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/048,190     | 05/30/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/050,935     | 05/30/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/048,101     | 05/30/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/048,356     | 05/30/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/056,250     | 08/29/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/056,296     | 08/29/97 |
| PCT/US98/10868                   | Non-provisional of                       | 60/056,293     | 08/29/97 |
| 10/100,683                       | Continuation-in-part of                  | PCT/US98/11422 | 06/04/98 |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,885     | 06/06/97 |
| PCT/US98/11422                   | Non-provisional of                       | 60/049,375     | 06/06/97 |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,881     | 06/06/97 |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,880     | 06/06/97 |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,896     | 06/06/97 |
| PCT/US98/11422                   | Non-provisional of                       | 60/049.020     | 06/06/97 |
| 101/05/0/11422                   | 1 TON PROTISIONAL OF                     | 100/017,020    | 00/00/97 |

| DCM 71000/11400                  |                                          | 1 (0/040.07)             | 0.000.00             |
|----------------------------------|------------------------------------------|--------------------------|----------------------|
| PCT/US98/11422                   | Non-provisional of                       | 60/048,876               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,895               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,884<br>60/048,894 | 06/06/97             |
| PCT/US98/11422<br>PCT/US98/11422 | Non-provisional of<br>Non-provisional of | 60/048,971               | 06/06/97<br>06/06/97 |
| PCT/US98/11422<br>PCT/US98/11422 | Non-provisional of                       | 60/048,964               | 06/06/97             |
| PCT/US98/11422                   |                                          | 60/048,882               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,899               | 06/06/97             |
| PCT/US98/11422<br>PCT/US98/11422 | Non-provisional of<br>Non-provisional of | 60/048,893               | 06/06/97             |
| PCT/US98/11422<br>PCT/US98/11422 | Non-provisional of                       | 60/048,990               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,900               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,892               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,915               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/049,019               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,970               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,972               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,916               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/049,373               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,875               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/049,374               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,917               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,949               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,974               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,883               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,897               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,898               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,962               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,963               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,877               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/048,878               | 06/06/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,645               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,642               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,668               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,635               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,627               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,667               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,666               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,764               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,643               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,769               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,763               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,650               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,584               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,647               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,661               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,662               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,646               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,654               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,651               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,644               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,765               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,762               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,775               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,648               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,774               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,649               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,770               | 09/05/97             |
| PCT/US98/11422                   | Non-provisional of                       | 60/057,771               | 09/05/97             |

| PCT/US98/11422 | Non-provisional of                         | 60/057,761     | 09/05/97 |
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| PCT/US98/11422 | Non-provisional of                         | 60/057,760     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/057,776     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/057,778     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/057,629     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/057,628     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/057,777     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/057,634     | 09/05/97 |
| PCT/US98/11422 | Non-provisional of                         | 60/070,923     | 12/18/97 |
| 10/100,683     | Continuation-in-part of                    | PCT/US01/05614 | 02/21/01 |
| PCT/US01/05614 | Non-provisional of                         | 60/184,836     | 02/24/00 |
| PCT/US01/05614 | Non-provisional of                         | 60/193,170     | 03/29/00 |
| 10/100,683     | Continuation-in-part of                    | PCT/US98/12125 | 06/11/98 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,547     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,548     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,549     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,550     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,566     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,606     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,607     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,608     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,609     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,610     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/049,611     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/050,901     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/052,989     | 06/13/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/051,919     | 07/08/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/055,984     | 08/18/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,665     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,668     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,669     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,750     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,971     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,972     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/058,975     | 09/12/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/060,834     | 10/02/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/060,841     | 10/02/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/060,844     | 10/02/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/060,865     | 10/02/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/061,059     | 10/02/97 |
| PCT/US98/12125 | Non-provisional of                         | 60/061,060     | 10/02/97 |
| 10/100,683     | Continuation-in-part of                    | 09/627,081     | 07/27/00 |
| 09/627,081     | Continuation of                            | 09/213,365     | 12/17/98 |
| 09/213,365     | Continuation-in-part of                    | PCT/US98/13608 | 06/30/98 |
| 10/100,683     | Continuation-in-part of                    | PCT/US98/13608 | 06/30/98 |
| PCT/US98/13608 | Non-provisional of                         | 60/051,480     | 07/01/97 |
| PCT/US98/13608 | Non-provisional of                         | 60/051,381     | 07/01/97 |
| PCT/US98/13608 | Non-provisional of                         | 60/058,663     | 09/12/97 |
| PCT/US98/13608 | Non-provisional of                         | 60/058,598     | 09/12/97 |
| 10/100,683     | Continuation-in-part of                    | 09/984,490     | 10/30/01 |
| 09/984,490     | Divisional of                              | 09/227,357     | 01/08/99 |
| 09/227,357     | Continuation-in-part of                    | PCT/US98/13684 | 07/07/98 |
| 10/100,683     | Continuation-in-part of                    | 09/983,802     | 10/25/01 |
| 09/983,802     | Continuation-in-part of                    | 09/227,357     | 10/25/01 |
| 09/227,357     | Continuation of<br>Continuation-in-part of | PCT/US98/13684 | 07/07/98 |
| 10/100,683     | Continuation-in-part of                    | 09/973,278     | 10/10/01 |
| 09/973,278     |                                            | 60/239,899     | 10/10/01 |
|                | Non-provisional of                         |                |          |
| 09/973,278     | Continuation-in-part of                    | 09/227,357     | 01/08/99 |

| 09/227,357       | Continuation-in-part of | PCT/US98/13684 | 07/07/98   |
|------------------|-------------------------|----------------|------------|
| 10/100,683       | Continuation-in-part of | PCT/US98/13684 | 07/07/98   |
| PCT/US98/13684   | Non-provisional of      | 60/051,926     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/052,793     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,925     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,929     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/052,803     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/052,732     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,931     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,932     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,916     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,930     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,930     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,920     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/052,733     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/052,755     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,919     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/051,919     | 07/08/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,722     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,723     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,948     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,949     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,953     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,950     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,947     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,964     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/056,360     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,684     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,984     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/055,954     | 08/18/97   |
| PCT/US98/13684   | Non-provisional of      | 60/058,785     | 09/12/97   |
| PCT/US98/13684   | Non-provisional of      | 60/058,785     | 09/12/97   |
| PCT/US98/13684   | Non-provisional of      | 60/058,660     | 09/12/97   |
| PCT/US98/13684   | Non-provisional of      | 60/058,661     | 09/12/97   |
| 10/100,683       | Continuation-in-part of | 09/776,724     | 02/06/01   |
| 09/776,724       | Non-provisional of      | 60/180,909     | 02/08/00   |
| 09/776,724       | Continuation-in-part of | 09/669,688     | 09/26/00   |
| 09/669.688       | Continuation of         | 09/229,982     | 01/14/99   |
| 09/229,982       | Continuation-in-part of | PCT/US98/14613 | 07/15/98   |
| 10/100,683       | Continuation-in-part of | 09/669,688     | 09/26/00   |
| 09/669,688       | Continuation of         | 09/229,982     | 01/14/99   |
| 09/229,982       | Continuation-in-part of | PCT/US98/14613 | 07/15/98   |
| 10/100,683       | Continuation-in-part of | 09/229.982     | 01/14/99   |
| 09/229,982       | Continuation-in-part of | PCT/US98/14613 | 07/15/98   |
| 10/100,683       | Continuation-in-part of | PCT/US98/14613 | 07/15/98   |
| PCT/US98/14613   | Non-provisional of      | 60/052,661     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,872     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,871     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,874     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,873     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,870     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,875     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/052,875     | 07/16/97   |
| PCT/US98/14613   | Non-provisional of      | 60/053,440     | 07/22/97   |
| PCT/US98/14613   | Non-provisional of      | 60/053,441     | 07/22/97   |
| PCT/US98/14613   | Non-provisional of      | 60/056,359     | 08/18/97   |
| PCT/US98/14613   | Non-provisional of      | 60/056,339     | 08/18/97   |
| PCT/US98/14613   | Non-provisional of      | 60/055,985     | 08/18/97   |
| 1 € 1/0390/14613 | 1 NOTE-PROVISIONAL OF   | L 00/02/362    | 1 06/18/97 |

| PCT/US98/14613 | N                                        | 60/055,952               | 08/18/97  |
|----------------|------------------------------------------|--------------------------|-----------|
| PCT/US98/14613 | Non-provisional of                       | 60/055,952               | 08/18/97  |
| PCT/US98/14613 | Non-provisional of<br>Non-provisional of | 60/056,361               | 08/18/97  |
| PCT/US98/14613 | Non-provisional of                       | 60/055,726               | 08/18/97  |
| PCT/US98/14613 | Non-provisional of                       | 60/055,724               | 08/18/97  |
| PCT/US98/14613 | Non-provisional of                       | 60/055,724               | 08/18/97  |
| PCT/US98/14613 |                                          | 60/055,683               | 08/18/97  |
| 10/100,683     | Non-provisional of                       |                          | 06/05/01  |
|                | Non-provisional of                       | 60/295,558<br>09/820,649 |           |
| 10/100,683     | Continuation-in-part of                  |                          | 03/30/01  |
| 09/820,649     | Continuation of                          | 09/666,984               | 09/21/00  |
| 09/666,984     | Continuation of                          | 09/236,557               | 01/26/99  |
| 09/236,557     | Continuation-in-part of                  | PCT/US98/15949           | 07/29/98  |
| 10/100,683     | Continuation-in-part of                  | PCT/US98/15949           | 07/29/98  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,212               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,209               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,234               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,218               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,214               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,236               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,215               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,211               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,217               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/054,213               | 07/30/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/055,968               | 08/18/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/055,969               | 08/18/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/055,972               | 08/18/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,561               | 08/19/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,534               | 08/19/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,729               | 08/19/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,543               | 08/19/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,727               | 08/19/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,554               | 08/19/97  |
| PCT/US98/15949 | Non-provisional of                       | 60/056,730               | 08/19/97  |
| 10/100,683     | Continuation-in-part of                  | 09/969,730               | 10/04/01  |
| 09/969,730     | Continuation-in-part of                  | 09/774,639               | 02/01/01  |
| 09/774,639     | Continuation of                          | 09/244,112               | 02/04/99  |
| 09/244,112     | Continuation-in-part of                  | PCT/US98/16235           | 08/04/98  |
| 10/100,683     | Continuation-in-part of                  | 09/774,639               | 02/01/01  |
| 09/774,639     | Continuation of                          | 09/244,112               | 02/04/99  |
| 09/244,112     | Continuation-in-part of                  | PCT/US98/16235           | 08/04/98  |
| 10/100,683     | Continuation-in-part of                  | 09/969,730               | 10/04/01  |
| 09/969,730     | Non-provisional of                       | 60/238,291               | 10/06/00  |
| 10/100,683     | Continuation-in-part of                  | PCT/US98/16235           | 08/04/98  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,386               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,807               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,312               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,309               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,798               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,310               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,806               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,809               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,804               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,803               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/054,808               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,311               | 08/05/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,986               | 08/18/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/055,970               | 08/18/97  |
| PCT/US98/16235 | Non-provisional of                       | 60/056,563               | 08/19/97  |
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|----------------------------------|-----------------------------------------------|-------------------------------|----------------------|
| PCT/US98/16235                   | Non-provisional of                            | 60/056,557                    | 08/19/97             |
| PCT/US98/16235                   | Non-provisional of                            | 60/056,731                    | 08/19/97             |
| PCT/US98/16235                   | Non-provisional of                            | 60/056,365                    | 08/19/97             |
| PCT/US98/16235                   | Non-provisional of                            | 60/056,367                    | 08/19/97<br>08/19/97 |
| PCT/US98/16235                   | Non-provisional of                            | 60/056,370                    | 08/19/97             |
| PCT/US98/16235<br>PCT/US98/16235 | Non-provisional of<br>Non-provisional of      | 60/056,364                    | 08/19/97             |
| PCT/US98/16235                   | Non-provisional of<br>Non-provisional of      | 60/056,366                    | 08/19/97             |
| PCT/US98/16235                   |                                               |                               |                      |
|                                  | Non-provisional of<br>Continuation-in-part of | 60/056,371                    | 08/19/97<br>11/17/00 |
| 10/100,683                       | Continuation-in-part of                       | 09/716,128<br>09/251,329      | 02/17/99             |
|                                  |                                               | PCT/US98/17044                | 08/18/98             |
| 09/251,329                       | Continuation-in-part of                       |                               |                      |
| 10/100,683<br>PCT/US98/17044     | Continuation-in-part of<br>Non-provisional of | PCT/US98/17044<br>60/056,555  | 08/18/98<br>08/19/97 |
| PCT/US98/17044<br>PCT/US98/17044 | Non-provisional of                            | 60/056,556                    | 08/19/97             |
| PCT/US98/17044                   |                                               | 60/056,535                    | 08/19/97             |
| PCT/US98/17044                   | Non-provisional of<br>Non-provisional of      | 60/056,629                    | 08/19/97             |
|                                  | Non-provisional of                            | 60/056,369                    |                      |
| PCT/US98/17044<br>PCT/US98/17044 | Non-provisional of                            | 60/056,369                    | 08/19/97<br>08/19/97 |
| PCT/US98/17044<br>PCT/US98/17044 | Non-provisional of<br>Non-provisional of      | 60/056,628                    | 08/19/97             |
| PCT/US98/17044                   | Non-provisional of                            | 60/056,368                    | 08/19/97             |
| PCT/US98/17044                   | Non-provisional of                            | 60/056,726                    | 08/19/97             |
| PCT/US98/17044                   | Non-provisional of                            |                               | 06/16/98             |
| PCT/US98/17044                   |                                               | 60/089,510                    | 07/15/98             |
| 10/100,683                       | Non-provisional of<br>Continuation-in-part of | 60/092,956<br>09/729,835      | 0//15/98             |
| 10/100,083                       | Continuation-in-part of                       | 09/129,835                    | 12/06/00             |
| 09/729,835                       | Divisional of                                 | 09/257,179                    | 02/25/99             |
| 09/257,179                       | Continuation-in-part of                       | PCT/US98/17709                | 08/27/98             |
| 10/100,683                       | Continuation-in-part of                       | 09/257,179                    | 08/27/98             |
| 10/100,003                       | Continuation-in-part or                       | 09/237,179                    | 02/25/99             |
| 09/257,179                       | Continuation-in-part of                       | PCT/US98/17709                | 08/27/98             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US98/17709                | 00/2//90             |
| 10/100,083                       | Continuation-in-part or                       | 101/0398/17/09                | 08/27/98             |
| PCT/US98/17709                   | Non-provisional of                            | 60/056,270                    | 08/29/97             |
| PCT/US98/17709                   | Non-provisional of                            | 60/056,271                    | 08/29/97             |
| PCT/US98/17709                   | Non-provisional of                            | 60/056,247                    | 08/29/97             |
| PCT/US98/17709                   | Non-provisional of                            | 60/056,073                    | 08/29/97             |
| 10/100,683                       | Continuation-in-part of                       | 10/047,021                    | 01/17/02             |
| 10/047,021                       | Continuation-in-part of                       | 09/722,329                    | 11/28/00             |
| 09/722,329                       | Continuation of                               | 09/262,109                    | 03/04/99             |
| 09/262,109                       | Continuation-in-part of                       | PCT/US98/18360                | 09/03/98             |
| 10/100,683                       | Continuation-in-part of                       | 09/722,329                    | 11/28/00             |
| 09/722,329                       | Continuation of                               | 09/262,109                    | 03/04/99             |
| 09/262,109                       | Continuation-in-part of                       | PCT/US98/18360                | 09/03/98             |
| 10/100,683                       | Continuation-in-part of                       | PZ016pct2                     | 01/17/02             |
| PZ016pct2                        | Non-provisional of                            | 60/262,066                    | 01/18/01             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US98/18360                | 09/03/98             |
| PCT/US98/18360                   | Non-provisional of                            | 60/057,626                    | 09/05/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/057,663                    | 09/05/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/057,669                    | 09/05/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/058,667                    | 09/12/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/058,974                    | 09/12/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/058,973                    | 09/12/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/058,666                    | 09/12/97             |
| PCT/US98/18360                   | Non-provisional of                            | 60/090,112                    | 06/22/98             |
| 10/100,683                       | Continuation-in-part of                       | 09/281,976                    | 03/31/99             |
| 09/281,976                       | Continuation-in-part of                       | PCT/US98/20775                | 10/01/98             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US98/20775                | 10/01/98             |
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| PCT/US98/20775                   | Non-provisional of                            | 60/060,837                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of                            | 60/060,862                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of                            | 60/060,839                   | 10/02/97             |
| PCT/US98/20775<br>PCT/US98/20775 | Non-provisional of                            | 60/060,866                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of<br>Non-provisional of      | 60/060,845                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of                            | 60/060,838                   | 10/02/97             |
| PCT/US98/20775                   |                                               | 60/060,874                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of<br>Non-provisional of      | 60/060,833                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of                            | 60/060,833                   | 10/02/97             |
| PCT/US98/20775                   | Non-provisional of                            | 60/060,880                   | 10/02/97             |
| 10/100,683                       | Continuation-in-part of                       | 09/984,429                   | 10/02/97             |
| 10/100,083                       | Continuation-m-part of                        | 09/984,429                   | 10/30/01             |
| 09/984,429                       | Non-provisional of                            | 60/244,591                   | 11/01/00             |
| 09/984,429                       | Continuation-in-part of                       | 09/288,143                   | 04/08/99             |
| 09/288,143                       | Continuation-in-part of                       | PCT/US98/21142               | 10/08/98             |
| 10/100,683                       | Non-provisional of                            | 60/244,591                   | 10/00/20             |
| 10/100,000                       | TKM-provisional or                            | 00/244,251                   | 11/01/00             |
| 10/100,683                       | Continuation-in-part of                       | 09/288,143                   | 04/08/99             |
| 09/288,143                       | Continuation-in-part of                       | PCT/US98/21142               | 10/08/98             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US98/21142               | 10/08/98             |
| PCT/US98/21142                   | Non-provisional of                            | 60/061,463                   | 10/09/97             |
| PCT/US98/21142                   | Non-provisional of                            | 60/061,529                   | 10/09/97             |
| PCT/US98/21142                   | Non-provisional of                            | 60/071,498                   | 10/09/97             |
| PCT/US98/21142                   | Non-provisional of                            | 60/061,527                   | 10/09/97             |
| PCT/US98/21142                   | Non-provisional of                            | 60/061,536                   | 10/09/97             |
| PCT/US98/21142                   | Non-provisional of                            | 60/061,532                   | 10/09/97             |
| 10/100,683                       | Continuation-in-part of                       | 09/296,622                   |                      |
|                                  |                                               |                              | 04/23/99             |
| 09/296,622                       | Continuation-in-part of                       | PCT/US98/22376               | 10/23/98             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US98/22376               | 10/23/98             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,099                   |                      |
|                                  |                                               | 4                            | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,088                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,100                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,387                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,148                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,386                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/062,784                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,091                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,090                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,089                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,092                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,111                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,101                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,109                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            | 60/063,110                   | 10/24/97             |
| PCT/US98/22376                   | Non-provisional of                            |                              |                      |
| PCT/US98/22376                   | Non-provisional of<br>Continuation-in-part of | 60/063,097                   | 10/24/97             |
| 09/974,879                       | Non-provisional of                            | 09/974,879<br>60/239,893     | 10/12/01             |
| 09/9/4,8/9                       | Non-provisional of<br>Continuation-in-part of |                              | 10/13/00 03/28/01    |
|                                  | Continuation-in-part of<br>Continuation of    | 09/818,683                   |                      |
| 09/818,683                       | Continuation of<br>Continuation-in-part of    | 09/305,736<br>PCT/US98/23435 | 05/05/99<br>11/04/98 |
| 09/305,736                       | Continuation-in-part of                       | 09/818,683                   | 03/28/01             |
| 09/818,683                       | Continuation-in-part of                       | 09/818,683                   | 05/05/99             |
| 09/305,736                       | Continuation of<br>Continuation-in-part of    | PCT/US98/23435               | 11/04/98             |
| 10/100,683                       | Continuation-in-part of                       | 09/305,736                   | 05/05/99             |
| 10/100,083                       | Communication-in-part of                      | 1 09/303,/30                 | 1 05/05/99           |

| 09/305,736             | Continuation-in-part of | PCT/US98/23435 | 11/04/98 |
|------------------------|-------------------------|----------------|----------|
| 10/100,683             | Continuation-in-part of | PCT/US98/23435 | 11/04/98 |
| PCT/US98/23435         | Non-provisional of      | 60/064,911     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,912     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,983     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,900     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,988     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,987     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,908     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,984     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/064,985     | 11/07/97 |
| PCT/US98/23435         | Non-provisional of      | 60/066,094     | 11/17/97 |
| PCT/US98/23435         | Non-provisional of      | 60/066,100     | 11/17/97 |
| PCT/US98/23435         | Non-provisional of      | 60/066,089     | 11/17/97 |
| PCT/US98/23435         | Non-provisional of      | 60/066,095     | 11/17/97 |
| PCT/US98/23435         | Non-provisional of      | 60/066,090     | 11/17/97 |
| 10/100,683             | Continuation-in-part of | 09/334,595     | 06/17/99 |
| 09/334,595             | Continuation-in-part of | PCT/US98/27059 | 12/17/98 |
| 10/100,683             | Continuation-in-part of | PCT/US98/27059 | 12/17/98 |
| PCT/US98/27059         | Non-provisional of      | 60/070,923     | 1        |
| T C I C D J SI I C C S | Troit provincian or     | 00,010,020     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,007     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,057     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,006     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,369     | 12/19/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,367     | 12/19/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,368     | 12/19/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,169     | 12/19/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,053     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,064     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,054     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,008     | 12/18/97 |
| PCT/US98/27059         | Non-provisional of      | 60/068,365     | 12/19/97 |
| 10/100,683             | Continuation-in-part of | 09/938,671     | 08/27/01 |
| 09/938,671             | Continuation of         | 09/739,907     | 12/20/00 |
| 09/739,907             | Continuation of         | 09/348,457     | 07/07/99 |
| 09/348,457             | Continuation-in-part of | PCT/US99/00108 | 01/06/99 |
| 10/100,683             | Continuation-in-part of | 09/739,907     | 12/20/00 |
| 09/739,907             | Continuation of         | 09/348,457     | 07/07/99 |
| 09/348,457             | Continuation-in-part of | PCT/US99/00108 | 01/06/99 |
| 10/100,683             | Continuation-in-part of | 09/348,457     | 07/07/99 |
| 09/348,457             | Continuation-in-part of | PCT/US99/00108 | 01/06/99 |
| 10/100,683             | Continuation-in-part of | PCT/US99/00108 | 01/06/99 |
| PCT/US99/00108         | Non-provisional of      | 60/070,704     |          |
|                        |                         |                | 01/07/98 |
| PCT/US99/00108         | Non-provisional of      | 60/070,658     |          |
|                        |                         |                | 01/07/98 |
| PCT/US99/00108         | Non-provisional of      | 60/070,692     |          |
|                        |                         |                | 01/07/98 |
| PCT/US99/00108         | Non-provisional of      | 60/070,657     |          |
|                        |                         |                | 01/07/98 |
| 10/100,683             | Continuation-in-part of | 09/949,925     | 09/12/01 |
| 09/949,925             | Non-provisional of      | 60/232,150     | 09/12/00 |
| 09/949,925             | Continuation-in-part of | PCT/US99/01621 | 01/27/99 |
| 09/949,925             | Continuation-in-part of | 09/363,044     | 07/29/99 |
| 09/363,044             | Continuation-in-part of | PCT/US99/01621 | 01/27/99 |
| 10/100,683             | Continuation-in-part of | 09/813,153     | 03/21/01 |
| 09/813,153             | Continuation of         | 09/363,044     | 07/29/99 |

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|----------------------------------|----------------------------------------------------|----------------------------------|-------------------|
| 09/363,044<br>10/100,683         | Continuation-in-part of<br>Continuation-in-part of | PCT/US99/01621<br>09/363,044     | 01/27/99 07/29/99 |
| 09/363,044                       | Continuation-in-part of                            | PCT/US99/01621                   | 01/29/99          |
| 10/100,683                       | Continuation-in-part of                            | PC1/US99/01621<br>PCT/US99/01621 | 01/27/99          |
|                                  | Non-provisional of                                 |                                  | 01/2//99          |
| PCT/US99/01621<br>PCT/US99/01621 |                                                    | 60/073,170                       | 01/30/98          |
| PCT/US99/01621                   | Non-provisional of<br>Non-provisional of           | 60/073,167<br>60/073,165         | 01/30/98          |
| PCT/US99/01621                   |                                                    | 60/073,165                       | 01/30/98          |
|                                  | Non-provisional of                                 |                                  | 01/30/98          |
| PCT/US99/01621<br>PCT/US99/01621 | Non-provisional of<br>Non-provisional of           | 60/073,162<br>60/073,161         | 01/30/98          |
|                                  |                                                    |                                  |                   |
| PCT/US99/01621<br>PCT/US99/01621 | Non-provisional of<br>Non-provisional of           | 60/073,160<br>60/073,159         | 01/30/98          |
| 10/100.683                       | Continuation-in-part of                            | 10/062.548                       | 01/30/98          |
| 10/100,083                       | Continuation-m-part of                             | 10/062,348                       | 02/05/02          |
| 10/062,548                       | Continuation of                                    | 09/369,247                       | 08/05/99          |
| 09/369,247                       | Continuation of                                    | PCT/US99/02293                   | 02/04/99          |
| 10/100,683                       | Continuation-in-part of                            | 09/369,247                       | 08/05/99          |
| 09/369,247                       | Continuation-in-part of                            | PCT/US99/02293                   | 02/04/99          |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/02293                   | 02/04/99          |
| PCT/US99/02293                   | Non-provisional of                                 | 60/074.118                       | 02/09/98          |
| PCT/US99/02293                   | Non-provisional of                                 | 60/074,115                       | 02/09/98          |
| PCT/US99/02293                   | Non-provisional of                                 | 60/074,037                       | 02/09/98          |
| PCT/US99/02293                   | Non-provisional of                                 | 60/074,141                       | 02/09/98          |
| PCT/US99/02293                   | Non-provisional of                                 | 60/074,141                       | 02/09/98          |
| 10/100,683                       | Continuation-in-part of                            | 09/716.129                       | 11/17/00          |
| 09/716.129                       | Continuation-in-part of                            | PCT/US99/03939                   | 02/24/99          |
| 09/716,129                       | CON                                                | 09/382,572                       | 08/25/99          |
| 09/382,572                       | Continuation-in-part of                            | PCT/US99/03939                   | 02/24/99          |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/03939                   | 02/24/99          |
| PCT/US99/03939                   | Non-provisional of                                 | 60/076.053                       | 02/26/98          |
| PCT/US99/03939                   | Non-provisional of                                 | 60/076,051                       | 02/26/98          |
| PCT/US99/03939                   | Non-provisional of                                 | 60/076,054                       | 02/26/98          |
| PCT/US99/03939                   | Non-provisional of                                 | 60/076,052                       | 02/26/98          |
| PCT/US99/03939                   | Non-provisional of                                 | 60/076,057                       | 02/26/98          |
| 10/100,683                       | Continuation-in-part of                            | 09/798,889                       |                   |
|                                  |                                                    |                                  | 03/06/01          |
| 09/798,889                       | CON                                                | 09/393.022                       | 09/09/99          |
| 09/393,022                       | Continuation-in-part of                            | PCT/US99/05721                   | 03/11/99          |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/05721                   | 03/11/99          |
| PCT/US99/05721                   | Non-provisional of                                 | 60/077,714                       | 03/12/98          |
| PCT/US99/05721                   | Non-provisional of                                 | 60/077,686                       | 03/12/98          |
| PCT/US99/05721                   | Non-provisional of                                 | 60/077,687                       | 03/12/98          |
| PCT/US99/05721                   | Non-provisional of                                 | 60/077,696                       | 03/12/98          |
| 10/100,683                       | Continuation-in-part of                            | 09/397,945                       |                   |
|                                  |                                                    |                                  | 09/17/99          |
| 09/397,945                       | Continuation-in-part of                            | PCT/US99/05804                   | 03/18/99          |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/05804                   | 03/18/99          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,566                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,576                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,573                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,574                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,579                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/080,314                       | 04/01/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/080,312                       | 04/01/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,578                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,581                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,577                       | 03/19/98          |
| PCT/US99/05804                   | Non-provisional of                                 | 60/078,563                       | 03/19/98          |

| PCT/US99/05804                   | Non-provisional of                                 | 60/080,313                       | 04/01/98             |
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| 10/100,683                       | Continuation-in-part of                            | 09/948,783                       | 09/10/01             |
| 09/948,783                       | Non-provisional of                                 | 60/231,846                       |                      |
|                                  |                                                    |                                  | 09/11/00             |
| 09/948,783                       | Continuation-in-part of                            | 09/892,877                       |                      |
|                                  |                                                    |                                  | 06/28/01             |
| 09/892,877                       | Continuation of                                    | 09/437,658                       | 11/10/00             |
| 09/437,658                       | Continuation-in-part of                            | PCT/US99/09847                   | 11/10/99<br>05/06/99 |
| 10/100,683                       | Continuation-in-part of                            | 09/892,877                       | 05/00/99             |
| 10/100,005                       | Continuation-in-part or                            | 09/092,077                       | 06/28/01             |
| 09/892,877                       | Continuation of                                    | 09/437,658                       | 00.20.01             |
|                                  |                                                    |                                  | 11/10/99             |
| 09/437,658                       | Continuation-in-part of                            | PCT/US99/09847                   | 05/06/99             |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/09847                   | 05/06/99             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,093                       | 05/12/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,094                       | 05/12/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,105                       | 05/12/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,180                       | 05/12/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,927                       | 05/18/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,906                       | 05/18/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,920                       | 05/18/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,924                       | 05/18/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,922                       | 05/18/98             |
| PCT/US99/09847                   | Non-provisional of                                 | 60/085,923                       | 05/18/98             |
| PCT/US99/09847<br>PCT/US99/09847 | Non-provisional of                                 | 60/085,921<br>60/085,925         | 05/18/98<br>05/18/98 |
| PCT/US99/09847                   | Non-provisional of<br>Non-provisional of           | 60/085,925                       | 05/18/98             |
| 10/100,683                       | Continuation-in-part of                            | 10/050,873                       | 05/18/98             |
| 10/050,873                       | Non-provisional of                                 | 60/263,681                       | 01/18/02             |
| 10/050,873                       | Non-provisional of                                 | 60/263,230                       | 01/23/01             |
| 10/050,873                       | Continuation-in-part of                            | 09/461,325                       | 12/14/99             |
| 09/461.325                       | Continuation-in-part of                            | PCT/US99/13418                   | 06/15/99             |
| 10/100.683                       | Continuation-in-part of                            | 10/012.542                       | 12/12/01             |
| 10/012,542                       | Divisional of                                      | 09/461.325                       | 12/14/99             |
| 09/461,325                       | Continuation-in-part of                            | PCT/US99/13418                   | 06/15/99             |
| 10/100,683                       | Continuation-in-part of                            | 09/461,325                       |                      |
| -                                |                                                    |                                  | 12/14/99             |
| 09/461,325                       | Continuation-in-part of                            | PCT/US99/13418                   | 06/15/99             |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/13418                   | 06/15/99             |
| PCT/US99/13418                   | Non-provisional of                                 | 60/089,507                       | 06/16/98             |
| PCT/US99/13418                   | Non-provisional of                                 | 60/089,508                       | 06/16/98             |
| PCT/US99/13418                   | Non-provisional of                                 | 60/089,509                       | 06/16/98             |
| PCT/US99/13418                   | Non-provisional of                                 | 60/089,510                       | 06/16/98             |
| PCT/US99/13418                   | Non-provisional of                                 | 60/090,112                       | 06/22/98             |
| PCT/US99/13418                   | Non-provisional of                                 | 60/090,113                       | 06/22/98             |
| 10/100,683                       | Continuation-in-part of                            | 09/984,271                       | 10/29/01             |
| 09/984,271                       | Divisional of                                      | 09/482,273                       | 01/13/00             |
| 09/482,273<br>10/100,683         | Continuation-in-part of                            | PCT/US99/15849<br>09/984.276     | 07/14/99<br>10/29/01 |
| 09/984.276                       | Continuation-in-part of<br>Divisional of           | 09/984,276                       | 01/13/00             |
| 09/984,276                       | Continuation-in-part of                            |                                  |                      |
| 10/100,683                       | Continuation-in-part of<br>Continuation-in-part of | PCT/US99/15849<br>09/482,273     | 07/14/99 01/13/00    |
| 09/482,273                       | Continuation-in-part of                            | PCT/US99/15849                   | 07/14/99             |
| 10/100,683                       | Continuation-in-part of                            | PCT/US99/15849<br>PCT/US99/15849 | 07/14/99             |
| PCT/US99/15849                   | Non-provisional of                                 | 60/092.921                       | 07/15/98             |
| PCT/US99/15849                   | Non-provisional of                                 | 60/092,922                       | 07/15/98             |
|                                  |                                                    |                                  | 0//13/90             |

| 10/100 (02                   | Ia                                            | Pomitigal income             | 00/24/01 |
|------------------------------|-----------------------------------------------|------------------------------|----------|
| 10/100,683<br>PCT/US01/29871 | Continuation-in-part of<br>Non-provisional of | PCT/US01/29871<br>60/234,925 | 09/24/01 |
| PCT/US01/29871               | Continuation-in-part of                       | PCT/US01/00911               | 01/12/01 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US01/00911               | 01/12/01 |
|                              |                                               |                              |          |
| PCT/US01/00911<br>10/100,683 | Continuation-in-part of                       | 09/482,273<br>60/350,898     | 01/13/00 |
|                              | Non-provisional of                            |                              | 01/25/02 |
| 10/100,683                   | Continuation-in-part of                       | 09/489,847                   | 01/24/00 |
| 09/489,847                   | Continuation-in-part of                       | PCT/US99/17130               | 07/29/99 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US99/17130               | 07/29/99 |
| PCT/US99/17130               | Non-provisional of                            | 60/094,657                   | 07/30/98 |
| PCT/US99/17130               | Non-provisional of                            | 60/095,486                   | 08/05/98 |
| PCT/US99/17130               | Non-provisional of                            | 60/096,319                   | 08/12/98 |
| PCT/US99/17130               | Non-provisional of                            | 60/095,454                   | 08/06/98 |
| PCT/US99/17130               | Non-provisional of                            | 60/095,455                   | 08/06/98 |
| 10/100,683                   | Continuation-in-part of                       | 10/054,988                   | 01/25/02 |
| 10/054,988                   | Continuation of                               | 09/904,615                   | 07/16/01 |
| 09/904,615                   | Continuation of                               | 09/739,254                   | 12/19/00 |
| 09/739,254                   | Continuation of                               | 09/511,554                   | 02/23/00 |
| 09/511,554                   | Continuation-in-part of                       | PCT/US99/19330               | 08/24/99 |
| 10/100,683                   | Continuation-in-part of                       | 09/904,615                   | 1        |
|                              |                                               |                              | 07/16/01 |
| 09/904,615                   | Continuation of                               | 09/739,254                   | 12/19/00 |
| 09/739,254                   | Continuation of                               | 09/511,554                   | 02/23/00 |
| 09/511,554                   | Continuation-in-part of                       | PCT/US99/19330               | 08/24/99 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US99/19330               | 08/24/99 |
| PCT/US99/19330               | Non-provisional of                            | 60/097,917                   | 08/25/98 |
| PCT/US99/19330               | Non-provisional of                            | 60/098,634                   | 08/31/98 |
| 10/100,683                   | Continuation-in-part of                       | 09/820,893                   | 03/30/01 |
| 09/820,893                   | Continuation of                               | 09/531,119                   | 03/20/00 |
| 09/531,119                   | Continuation-in-part of                       | PCT/US99/22012               | 09/22/99 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US99/22012               | 09/22/99 |
| PCT/US99/22012               | Non-provisional of                            | 60/101,546                   | 09/23/98 |
| PCT/US99/22012               | Non-provisional of                            | 60/102,895                   | 10/02/98 |
| 10/100,683                   | Continuation-in-part of                       | 09/948,820                   | 09/10/01 |
| 09/948,820                   | Continuation of                               | 09/565,391                   | 05/05/00 |
| 09/565,391                   | Continuation-in-part of                       | PCT/US99/26409               | 11/09/99 |
| 10/100,683                   | Continuation-in-part of                       | 09/565,391                   | 05/05/00 |
| 09/565,391                   | Continuation-in-part of                       | PCT/US99/26409               | 11/09/99 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US99/26409               | 11/09/99 |
| PCT/US99/26409               | Non-provisional of                            | 60/108,207                   | 11/12/98 |
| 10/100,683                   | Continuation-in-part of                       | 09/895,298                   | 07/02/01 |
| 09/895,298                   | Continuation of                               | 09/591,316                   | 06/09/00 |
| 09/591,316                   | Continuation-in-part of                       | PCT/US99/29950               | 12/16/99 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US99/29950               | 12/16/99 |
| PCT/US99/29950               | Non-provisional of                            | 60/113,006                   | 12/18/98 |
| PCT/US99/29950               | Non-provisional of                            | 60/112,809                   | 12/17/98 |
| 10/100,683                   | Continuation-in-part of                       | 09/985,153                   | 11/01/01 |
| 09/985,153                   | Continuation of                               | 09/618,150                   | 07/17/00 |
| 09/618,150                   | Continuation-in-part of                       | PCT/US00/00903               | 01/18/00 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US00/00903               | 01/18/00 |
| PCT/US00/00903               | Non-provisional of                            | 60/116,330                   | 01/19/99 |
| 10/100,683                   | Continuation-in-part of                       | 09/997,131                   | 1        |
|                              |                                               |                              | 11/30/01 |
| 09/997,131                   | Continuation of                               | 09/628,508                   | 07/28/00 |
| 09/628,508                   | Continuation-in-part of                       | PCT/US00/03062               | 02/08/00 |
| 10/100,683                   | Continuation-in-part of                       | PCT/US00/03062               | 02/08/00 |
| PCT/US00/03062               | Non-provisional of                            | 60/119,468                   | 02/10/99 |
| 10/100,683                   | Continuation-in-part of                       | 10/050,882                   | 01/18/02 |

| 10/050,882     | Continuation of          | 09/661,453     | 09/13/00 |
|----------------|--------------------------|----------------|----------|
| 09/661,453     | Continuation in-part of  | PCT/US00/06783 | 03/16/00 |
| 10/100,683     | Continuation-in-part of  | 09/661,453     | 00/10/00 |
| 10/100,000     | Communication in part of | 35,004,100     | 09/13/00 |
| 09/661,453     | Continuation-in-part of  | PCT/US00/06783 | 03/16/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/06783 | 03/16/00 |
| PCT/US00/06783 | Non-provisional of       | 60/125,055     | 03/18/99 |
| 10/100,683     | Continuation-in-part of  | 10/050,704     | 01/18/02 |
| 10/050,704     | Continuation of          | 09/684,524     | 10/10/00 |
| 09/684,524     | Continuation-in-part of  | PCT/US00/08979 | 04/06/00 |
| 10/100,683     | Continuation-in-part of  | 09/684,524     | 10/10/00 |
| 09/684,524     | Continuation-in-part of  | PCT/US00/08979 | 04/06/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/08979 | 04/06/00 |
| PCT/US00/08979 | Non-provisional of       | 60/128,693     | 04/09/99 |
| PCT/US00/08979 | Non-provisional of       | 60/130,991     | 04/26/99 |
| 10/100,683     | Continuation-in-part of  | 10/042,141     | 01/11/02 |
| 10/042,141     | Continuation of          | 09/726,643     | 12/01/00 |
| 09/726,643     | Continuation-in-part of  | PCT/US00/15187 | 06/02/00 |
| 10/100,683     | Continuation-in-part of  | 09/726,643     | 12/01/00 |
| 09/726,643     | Continuation-in-part of  | PCT/US00/15187 | 06/02/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/15187 | 06/02/00 |
| PCT/US00/15187 | Non-provisional of       | 60/137,725     | 06/07/99 |
| 10/100,683     | Continuation-in-part of  | 09/756,168     | 01/09/01 |
| 09/756,168     | Continuation-in-part of  | PCT/US00/19735 | 07/23/99 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/19735 | 07/20/00 |
| PCT/US00/19735 | Non-provisional of       | 60/145,220     | 07/23/99 |
| 10/100,683     | Continuation-in-part of  | PZ042P1C1      | 02/01/02 |
| PZ042P1C1      | Continuation of          | 09/781,417     | 02/13/01 |
| 09/781,417     | Continuation-in-part of  | PCT/US00/22325 | 08/16/00 |
| 10/100,683     | Continuation-in-part of  | 09/781,417     | 02/13/01 |
| 09/781,417     | Continuation-in-part of  | PCT/US00/22325 | 08/16/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/22325 | 08/16/00 |
| PCT/US00/22325 | Non-provisional of       | 60/149,182     | 08/17/99 |
| 10/100,683     | Continuation-in-part of  | 09/789,561     | 02/22/01 |
| 09/789,561     | Continuation-in-part of  | PCT/US00/24008 | 08/31/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/24008 | 08/31/00 |
| PCT/US00/24008 | Non-provisional of       | 60/152,315     | 09/03/99 |
| PCT/US00/24008 | Non-provisional of       | 60/152,317     | 09/03/99 |
| 10/100,683     | Continuation-in-part of  | 09/800,729     | 03/08/01 |
| 09/800,729     | Continuation-in-part of  | PCT/US00/26013 | 09/22/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/26013 | 09/22/00 |
| PCT/US00/26013 | Non-provisional of       | 60/155,709     | 09/24/99 |
| 10/100,683     | Continuation-in-part of  | 09/832,129     | 04/11/01 |
| 09/832,129     | Continuation-in-part of  | PCT/US00/28664 | 10/17/00 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/28664 | 10/17/00 |
| PCT/US00/28664 | Non-provisional of       | 60/163,085     | 11/02/99 |
| PCT/US00/28664 | Non-provisional of       | 60/172,411     | 12/17/99 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/29363 | 10/25/00 |
| PCT/US00/29363 | Non-provisional of       | 60/215,139     | 06/30/00 |
| PCT/US00/29363 | Non-provisional of       | 60/162,239     | 10/29/99 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/29360 | 10/25/00 |
| PCT/US00/29360 | Non-provisional of       | 60/215,138     | 06/30/00 |
| PCT/US00/29360 | Non-provisional of       | 60/162,211     | 10/29/99 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/29362 | 10/25/00 |
| PCT/US00/29362 | Non-provisional of       | 60/215,131     | 06/30/00 |
| PCT/US00/29362 | Non-provisional of       | 60/162,240     | 10/29/99 |
| 10/100,683     | Continuation-in-part of  | PCT/US00/29365 | 10/25/00 |
| PCT/US00/29365 | Non-provisional of       | 60/219,666     | 07/21/00 |

| PCT/US00/29365                   | Non-provisional of                            | 60/162,237                   | 10/29/99             |
|----------------------------------|-----------------------------------------------|------------------------------|----------------------|
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/29364               | 10/25/00             |
| PCT/US00/29364                   | Non-provisional of                            | 60/215,134                   | 06/30/00             |
| PCT/US00/29364                   | Non-provisional of                            | 60/162,238                   | 10/29/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30040               | 11/01/00             |
| PCT/US00/30040                   | Non-provisional of                            | 60/215,130                   | 06/30/00             |
| PCT/US00/30040                   | Non-provisional of                            | 60/163,580                   | 11/05/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30037               | 11/01/00             |
| PCT/US00/30037                   | Non-provisional of                            | 60/215,137                   | 06/30/00             |
| PCT/US00/30037                   | Non-provisional of                            | 60/163,577                   | 11/05/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30045               | 11/01/00             |
| PCT/US00/30045                   | Non-provisional of                            | 60/215,133                   | 06/30/00             |
| PCT/US00/30045                   | Non-provisional of                            | 60/163,581                   | 11/05/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30036               | 11/01/00             |
| PCT/US00/30036                   | Non-provisional of                            | 60/221,366                   | 07/27/00             |
| PCT/US00/30036                   | Non-provisional of                            | 60/163,576                   | 11/05/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30039               | 11/01/00             |
| PCT/US00/30039                   | Non-provisional of                            | 60/221,367                   | 07/27/00             |
| PCT/US00/30039                   | Non-provisional of                            |                              | 04/07/00             |
| PCT/US00/30039                   | Non-provisional of                            | 60/195,296<br>60/164,344     | 11/09/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30654               | 11/08/00             |
| PCT/US00/30654                   |                                               |                              |                      |
|                                  | Non-provisional of                            | 60/221,142                   | 07/27/00             |
| PCT/US00/30654                   | Non-provisional of                            | 60/164,835                   | 11/12/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30628               | 11/08/00             |
| PCT/US00/30628                   | Non-provisional of                            | 60/215,140                   | 06/30/00             |
| PCT/US00/30628                   | Non-provisional of                            | 60/164,744                   | 11/12/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30653               | 11/08/00             |
| PCT/US00/30653                   | Non-provisional of                            | 60/221,193                   | 07/27/00             |
| PCT/US00/30653                   | Non-provisional of                            | 60/164,735                   | 11/12/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30629               | 11/08/00             |
| PCT/US00/30629                   | Non-provisional of                            | 60/222,904                   | 08/03/00             |
| PCT/US00/30629                   | Non-provisional of                            | 60/164,825                   | 11/12/99             |
| 10/100,683<br>PCT/US00/30679     | Continuation-in-part of                       | PCT/US00/30679               |                      |
|                                  | Non-provisional of                            | 60/224,007                   | 08/04/00             |
| PCT/US00/30679                   | Non-provisional of                            | 60/164,834                   |                      |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/30674               | 11/08/00             |
| PCT/US00/30674<br>PCT/US00/30674 | Non-provisional of                            | 60/215,128                   | 06/30/00             |
|                                  | Non-provisional of                            | 60/164,750                   | 11/12/99             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US00/31162               | 11/15/00             |
| 60/215,136                       | Non-provisional of                            | 60/215,136                   | 06/30/00             |
| 60/215,136<br>10/100,683         | Non-provisional of<br>Continuation-in-part of | 60/166,415<br>PCT/US00/31282 | 11/19/99<br>11/15/00 |
| PCT/US00/31282                   | Non-provisional of                            | 60/219,665                   | 07/21/00             |
|                                  | Non-provisional of<br>Non-provisional of      |                              |                      |
| PCT/US00/31282<br>10/100,683     | Continuation-in-part of                       | 60/166,414<br>PCT/US00/30657 | 11/19/99             |
|                                  | Non-provisional of                            |                              |                      |
| PCT/US00/30657<br>PCT/US00/30657 | Non-provisional of<br>Non-provisional of      | 60/215,132                   | 06/30/00             |
|                                  | Continuation-in-part of                       | 60/164,731                   | 01/17/01             |
| 10/100,683                       |                                               | PCT/US01/01396               |                      |
| 60/256,968                       | Non-provisional of                            | 60/256,968<br>60/226,280     | 12/21/00 08/18/00    |
| 60/256,968                       | Non-provisional of                            |                              |                      |
| 10/100,683                       | Continuation-in-part of                       | PCT/US01/01387               | 01/17/01             |
| 60/259,803                       | Non-provisional of                            | 60/259,803                   | 01/05/01             |
| 60/259,803                       | Non-provisional of                            | 60/226,380                   | 08/18/00             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US01/01567               | 01/17/01             |
| PCT/US01/01567                   | Non-provisional of                            | 60/228,084                   | 08/28/00             |
| 10/100,683                       | Continuation-in-part of                       | PCT/US01/01431               | 01/17/01             |
| PCT/US01/01431                   | Non-provisional of                            | 60/231,968                   | 09/12/00             |
| PCT/US01/01431                   | Continuation-in-part of                       | 09/915,582                   | 07/27/01             |

|                | Continuation-in-part of | PCT/US01/01432                | 01/17/01 |
|----------------|-------------------------|-------------------------------|----------|
|                | Non-provisional of      | 60/236,326                    | 09/29/00 |
|                | Continuation-in-part of | PCT/US01/00544                | 01/09/01 |
|                | Non-provisional of      | 60/234,211                    | 09/20/00 |
|                | Continuation-in-part of | PCT/US01/01435                | 01/17/01 |
|                | Non-provisional of      | 60/226,282                    | 08/18/00 |
|                | Continuation-in-part of | PCT/US01/01386                | 01/17/01 |
|                | Non-provisional of      | 60/232,104                    | 09/12/00 |
|                | Continuation-in-part of | PCT/US01/01565                | 01/17/01 |
|                | Non-provisional of      |                               |          |
|                |                         | 60/234,210<br>PCT #1901/01204 | 09/20/00 |
|                | Continuation-in-part of | PCT/US01/01394                | 01/17/01 |
|                | Non-provisional of      | 60/259,805                    | 01/05/01 |
|                | Non-provisional of      | 60/226,278                    | 08/18/00 |
|                | Continuation-in-part of | PCT/US01/01434                | 01/17/01 |
|                | Non-provisional of      | 60/259,678                    | 01/05/01 |
|                | Non-provisional of      | 60/226,279                    | 08/18/00 |
|                | Continuation-in-part of | PCT/US01/01397                | 01/17/01 |
|                | Non-provisional of      | 60/226,281                    | 08/18/00 |
|                | Continuation-in-part of | PCT/US01/01385                | 01/17/01 |
| PCT/US01/01385 | Non-provisional of      | 60/231,969                    | 09/12/00 |
| 10/100,683     | Continuation-in-part of | PCT/US01/01384                | 01/17/01 |
| PCT/US01/01384 | Non-provisional of      | 60/259,516                    | 01/04/01 |
| PCT/US01/01384 | Non-provisional of      | 60/228,086                    | 08/28/00 |
| 10/100,683     | Continuation-in-part of | PCT/US01/01383                | 01/17/01 |
| PCT/US01/01383 | Non-provisional of      | 60/259,804                    | 01/05/01 |
| PCT/US01/01383 | Non-provisional of      | 60/228,083                    | 08/28/00 |
| 10/100,683     | Continuation-in-part of | PCT/US02/05064                | 02/21/02 |
| PCT/US02/05064 | Non-provisional of      | 60/304,444                    | 07/12/01 |
| PCT/US02/05064 | Non-provisional of      | 60/270,658                    | 02/23/01 |
|                | Continuation-in-part of | PCT/US02/05301                | 02/21/02 |
|                | Non-provisional of      | 60/304.417                    | 07/12/01 |
|                | Non-provisional of      | 60/270,625                    | 02/23/01 |
|                | Non-provisional of      | 60/304,121                    | 07/11/01 |
|                | Non-provisional of      | 60/295,869                    | 06/06/01 |
|                | Non-provisional of      | 60/325,209                    | 09/28/01 |
|                | Non-provisional of      | 60/311.085                    | 08/10/01 |
|                | Non-provisional of      | 60/330,629                    | 10/26/01 |
|                | Non-provisional of      | 60/331,046                    | 11/07/01 |
|                | Non-provisional of      | 60/358,554                    | 02/22/02 |
|                | Non-provisional of      | 60/358,714                    | 02/25/02 |

<sup>;</sup> wherein each of the above applications are all herein incorporated by reference in their entirety.

### Field of the Invention

100021 The present invention relates to human secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus and conditions related thereto. Antibodies that bind these polypeptides are also encompassed by the present invention. Also encompassed by the invention are vectors, host cells, and recombinant and synthetic methods for producing said polymucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polymucleotides and polypeptides of the invention. The present invention further encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

### Background of the Invention

[0003] Over the past few decades, an increasing percentage of the population has become diabetic. Diabetes mellitus is categorized into two types: Type I, known as Insulin-Dependent Diabetes Mellitus (IDDM), or Type II, known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM). IDDM is an autoimmune disorder in which the insulin-secreting pancreatic beta cells of the islets of Langerhans are destroyed. In these individuals, recombinant insulin therapy is employed to maintain glucose homeostasis and normal energy metabolism. NIDDM, on the other hand, is a polygenic disorder with no one gene responsible for the progression of the disease.

In NIDDM, insulin resistance eventually leads to the abolishment of insulin secretion resulting in insulin deficiency. Insulin resistance, at least in part, ensues from a block at the level of glucose uptake and phosphorylation in humans. Diabetics demonstrate a decrease in expression in adipose tissue of insulin-receptor substrate I ("IRSI") (Carvalho et al., FASEB J 13(15):2173-8 (1999)), glucose transporter 4 ("GLUT4") (Garvey et al., Diabetes 41(4):465-75 (1992)), and the novel abundant protein M gene transcript I ("apM1") (Stantick et al., Int J Exp Diabetes 1(2): 81-8 (2000)), as well as other as of yet unidentified factors. Insulin deficiency in NIDDM leads to failure of normal pancreatic beta-cell function and eventually to pancreatic-beta cell death.

[0005] Insulin affects fat, muscle, and liver. Instilin is the major regulator of energy metabolism. Malfunctioning of any step(s) in insulin secretion and/or action can lead to many disorders, including for example the dysregulation of oxygen utilization, adipogenesis, glycogenesis, glycogenesis, glucose uptake, protein synthesis, thermogenesis, and maintenance of the basal metabolic rate. This malfunctioning results in diseases and/or disorders that include, but are not limited to, hyperinsulinemia, insulin resistance, insulin deficiency. hyperlycemia, hyperlindemia, hyperchetonemia, and diabetes.

10006 Numerous debilitating diabetes-related secondary effects include, but are not limited to, obesity, forms of blindness (cataracts and diabetic retinopathy), limb amputations, kidney failure, fatty liver, coronary artery disease, and neuropathy.

10007] Some of the current drugs used to treat insulin resistance and/or diabetes (e.g., insulin secratogogues – sulfonylurea, insulin sensitizers – thiazolidenediones and metformin, and alpha-glucosidase and lipase inhibitors) are inadequate due to the dosage amounts and frequency with which they have to be administered as a result of poor pharmacokinetic properties, the lack of effective control over blood sugar levels, and potential side effects, among other reasons. Diabetes Therapeutic proteins in their native state or when recombinantly produced exhibit a rapid in vivo clearance. Typically, significant amounts of therapeutics are required to be effective during therapy. In addition, small molecules smaller than the 20 kDa range can be readily filtered through the renal tubules (glomerulus) leading to dose-dependent nephrotoxicity. Therefore, there is a need for improvement in treatment (e.g., a need for prolonging the effects of therapeutics of diabetes and/or diabetes related conditions).

### Summary of the Invention

100081 The present invention encompasses buman secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus and conditions related thereto. Antibodies that bind these polypeptides are also encompassed by the present invention; as are vectors, host cells, and recombinant and synthetic methods for producing said polymucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polymucleotides and polypeptides of the invention. The present invention also encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

#### Detailed Description

# Polynucleotides and Polypeptides of the Invention

Description of Table 1A

Table 1A summarizes information concerning certain polypnucleotides and polypeptides of the [0009] invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCCTM Deposit No:Z and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column, the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEO ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh column) and the "3' NT of Clone Seq." (eighth column) of SEO ID NO:X. In the ninth column, the nucleotide position of SEO ID NO:X of the putative start codon (methionine) is identified as "5" NT of Start Codon." Similarly, in column ten, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5" NT of First AA of Signal Pep." In the eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF".

[10011] SEQ ID NO:X (where X may be any of the polymedeotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby

enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table IA and/or elsewhere herein

[0012] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC™, as set forth in Table 1A. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

10014 The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

[9015] Also provided in Table 1.A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

1. Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Bluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988), Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene.

Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into E. coli strain XL-1 Blue, also available from Stratagene

[0017] Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., Focus 15:59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR\*2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available

from Life Technologies. See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO.X, SEQ ID NO.Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Mso provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences disclosed herein or the clones deposited with the ATCC™. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

100201 The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC™ Deposit No.Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:X, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC™ deposit No.Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA contained in ATCC™ Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC™ Deposit No.Z.

# Description of Table 1B (Comprised of Tables 1B.1 and 1B.2)

10021] Table 1B.1 and Table 1B.2 summarize some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID-), contig sequences (contig identifier (Contig ID-) and contig nucleotide sequence identifiers (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column of Tables 1B.1 and 1B.2 provide the gene numbers in the application for each clone identifier. The second column of Tables 1B.1 and 1B.2 provide unique clone identifiers, "Clone ID:", for cDNA clones related to each contig sequence disclosed in Table 1A and/or Table 1B. The third column of Tables 1B.1 and 1B.2 provide unique contig identifiers, "Contig ID:" for each of the contig sequences disclosed in these tables. The fourth column of Tables 1B.1 and 1B.2 provide the sequence identifiers, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1A and/or 1B.

### Table 1B.1

[0022] The fifth column of Table IB.1, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineates the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table IB.1 as SEO ID NO:Y (column 6). Column 7 of Table IB.1 lists residues comprising predicted

epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEO ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1B.1 as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1B.1. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 8 of Table 1B.1 ("Tissue Distribution") is described below in Table 1B.2 Column 5. Column 9 of Table 1B.1 ("Cytologic Band") provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIMTM, McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000, World Wide Web URL: www.ncbi.nlm.nih.gov/omim/). If the putative chromosomal location of the Ouery overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in Table 1B.1, column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

## Table 1B.2

[0023] Column 5 of Table 1B.2, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first code number shown in Table 1B.2 column 5 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. The second number in column 5 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEO ID NO:X) was identified in the corresponding tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array, cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of <sup>33</sup>P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between

the different hybridizations. The value presented after "[array code]." represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

#### Description of Table 1C

10024 Table 1C summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID), contig sequences (contig identifier (Contig ID) contig mucleotide sequence identifiers (SEQ ID NO.X)), and genomic sequences (SEQ ID NO.B). The first column provides a unique clone identifier, "Clone ID.", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO.X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID." for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO.X" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO.B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO.B which delineate certain polynucleotides of the invention (i.e., polypeptides containing amino acid sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

## Description of Table 1D

Table 1D: In preferred embodiments, the present invention encompasses a method of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) represented by Table 1A, Table 1B, and Table 1C, in an amount effective to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate the disease or disorder.

As indicated in Table 1D, the polynucleotides, polypeptides, agonists, or antagonists of the present invention (including antibodies) can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists thereof (including antibodies) could be used to treat the associated disease.

Table 1D provides information related to biological activities for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information related to assay which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID.") provides the unique clone identifier for each clone as previously described and indicated in Tables 1A, 1B, and 1C. The third column ("AA SEO ID NO:Y")

indicates the Sequence Listing SEO ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, 1B, and 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity. Table 1D describes the use of FMAT technology, inter alia, for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT) is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound flurophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. See, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using flourometric microvolume assay technology," Journal of Biomolecular Screening: 4:193-204 (1999). In particular, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)).

10028] Table 1D also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK, EKK, and p38 Kinase Activities" Biol. Chem. 379(8-9): 1101-1110 (1998).

### Description of Table 1E

Polymeleotides encoding polypeptides of the present invention can be used in assays to test for one or more biological activities. One such biological activity which may be tested includes the ability of polynucleotides and polypeptides of the invention to stimulate up-regulation or down-regulation of expression of particular genes and proteins. Hence, if polynucleotides and polypeptides of the present invention exhibit activity in altering particular gene and protein expression patterns, it is likely that these polynucleotides and polypeptides of the present invention may be involved in, or capable of effecting changes in, diseases associated with the altered sene and protein expression profiles. Hence, polynucleotides, polypeptides, or antibodies of the present invention could be used to treat said associated diseases.

TAQMAN® assays may be performed to assess the ability of polynucleotides (and polypeptides they encode) to alter the expression pattern of particular "target" genes. TAQMAN® reactions are performed to evaluate the ability of a test agent to induce or repress expression of specific genes in different cell types. TAQMAN® gene expression quantification assays ("TAQMAN® assays") are well known to, and routinely performed by, those of ordinary skill in the art. TAQMAN® assays are performed in a two step reverse transcription / polymerase chain reaction (RT-PCR). In the first (RT) step, cDNA is reverse transcribed from total RNA samples using random hexamer primers. In the second (PCR) step, PCR products are synthesized from the cDNA using gene specific primers.

10031] To quantify gene expression the TAQMAN® PCR reaction exploits the 5' nuclease activity of AMPLITAQ GOLD® DNA Polymerase to cleave a TAQMAN® probe (distinct from the primers) during PCR. The TAQMAN® probe contains a reporter dye at the 5'-end of the probe and a quencher dye at the 3' end of the probe and a quencher dye at the 3' end of the probe and the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter interest is present, the probe specifically anneals between the forward and reverse primer sites. AMPLITAQ GOLD® DNA Polymerase then cleaves the probe between the reporter and quencher when the probe hybridizes to the target, resulting in increased fluorescence of the reporter (see Figure 2). Accumulation of PCR products is detected directly by monitoring the increase in fluorescence of the reporter dve.

10032] After the probe fragments are displaced from the target, polymerization of the strand continues. The 3'-end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. The increase in fluorescence signal is detected only if the target sequence is complementary to the probe and is amplified during PCR. Because of these requirements, any nonspecific amplification is not detected.

10033] For test sample preparation, vector controls or constructs containing the coding sequence for the gene of interest are transfected into cells, such as for example 293T cells, and supermatants collected after 48 hours. For cell treatment and RNA isolation, multiple primary human cells or human cell lines are used; such cells may include but are not limited to, Normal Human Dermal Fibroblasts, Aortic Smooth Muscle, Human Umbilical Vein Endothelial Cells, HepG2, Daudi, Jurkat, U937, Caco, and THP-1 cell lines. Cells are plated in growth media and growth is arrested by culturing without media change for 3 days, or by switching cells to low serum media and incubating overnight. Cells are treated for 1, 6, or 24 hours with either vector control supermatant or sample supermatant (or purified/partially purified protein preparations in buffer). Total RNA is isolated; for example, by using Trizol extraction or by using the Ambion RNAqueous #-4PCR RNA isolation system. Expression levels of multiple genes are analyzed using TAQMAN®, and expression in the test sample is compared to control vector samples to identify genes induced or repressed. Each of the above described techniques are well known to, and routinely performed by, those of ordinary skill in the art.

10034 Table IE indicates particular disease classes and preferred indications for which polymucleotides, polypeptides, or antibodies of the present invention may be used in detecting, diagnosing, preventing, treating and/or ameliorating said diseases and disorders based on "target" gene expression patterns which may be up- or down-regulated by polynucleotides (and the encoded polypeptides) corresponding to each indicated cDNA Clone ID (shown in Table 1E, Column 2).

19035] Thus, in preferred embodiments, the present invention encompasses a method of detecting, diagnosing, preventing, treating, and/or ameliorating a disease or disorder listed in the "Disease Class" and/or "Preferred Indication" columns of Table IE; comprising administering to a patient in which such detection, diagnosis, prevention, or treatment is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, diagnose, prevent, treat, or ameliorate the disease or disorder. The first and second columns of Table ID show the "Gene No." and "eDNA Clone ID No.", respectively, indicating certain nucleic acids and proteins (or antibodies against the same) of the invention (including polynucleotide, polypeptide, and antibody fragments or variants thereof) that may be used in detecting, diagnosing, preventing, treating, or ameliorating the disease(s) or disorder(s) indicated in the corresponding row in the "Disease Class" or "Preferred Indication" Columns of Table 1E.

[0036] In another embodiment, the present invention also encompasses methods of detecting, diagnosing, preventing, treating, or ameliorating a disease or disorder listed in the "Disease Class" or "Preferred Indication" Columns of Table IE; comprising administering to a patient combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in the "Disease Class" or "Preferred Indication" Columns of Table IE.

[10037] The "Disease Class" Column of Table 1E provides a categorized descriptive heading for diseases, disorders, and/or conditions (more fully described below) that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

[0038] The "Preferred Indication" Column of Table IE describes diseases, disorders, and/or conditions that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or frazment or variant thereof).

10039] The "Cell Line" and "Exemplary Targets" Columns of Table 1E indicate particular cell lines and target genes, respectively, which may show altered gene expression patterns (i.e., up- or down-regulation of the indicated target gene) in Taqunan assays, performed as described above, utilizing polynucleotides of the cDNA Clone ID shown in the corresponding row. Alteration of expression patterns of the indicated "Exemplary Target" genes is correlated with a particular "Disease Class" and/or "Preferred Indication" as shown in the corresponding row under the respective column headings.

[0040] The "Exemplary Accessions" Column indicates GenBank Accessions (available online through the National Center for Biotechnology Information (NCBI) at www.ncbi.nlm.nih.gov/) which correspond to the "Exemplary Tarests" shown in the adiacent row.

[0041] The recitation of "Cancer" in the "Disease Class" Column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof) may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate neoplastic diseases and/or disorders (e.g., leukemias, cancers, etc., as described below under "Hyperproliferative Disorders").

[0042] The recitation of "Immune" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity" "Cardiovascular Disorders" and/or "Blood-Related Disorders"), and infections (e.g., as described below under "Infectious Disease").

The recitation of "Angiogenesis" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or amcliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), diseases and/or disorders of the cardiovascular system (e.g., as described below under "Cardiovascular Disorders"), diseases and/or disorders involving cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level"), diseases and/or disorders involving angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity"), to promote or inhibit cell or tissue regeneration (e.g., as described below under "Regeneration"), or to promote wound healing (e.g., as described below under "Wound Healing and Epithelial Cell Proliferation").

[10044] The recitation of "Diabetes" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diabetes (including diabetes mellitus types I and II), as well as diseases and/or disorders associated with, or consequential to, diabetes (e.g. as described below under "Endocrine Disorders," "Renal Disorders," and "Gastrointestinal Disorders").

Table 2 summarizes homology and features of some of the polypeptides of the invention. The 100451 first column provides a unique clone identifier. "Clone ID:", corresponding to a cDNA clone disclosed in Table 1A or Table 1B. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1B and allowing for correlation with the information in Table 1B. The third column provides the sequence identifier, "SEO ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth columns. In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

## Description of Table 3

Description of Table 2

[0046] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA

clone related to contig sequences disclosed in Table 1B. The second column provides the sequence identifier, "SEO ID NO:X", for contig sequences disclosed in Table 1A and/or Table 1B. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1B. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEO ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEO ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

### Description of Table 4

10471 Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B.2, column 5. Column 1 provides the tissue/cell source identifier code disclosed in Table 1B.2, Column 5. Columns 2-5 provide a description of the tissue or cell source. Note that "Description" and "Tissue" sources (i.e. columns 2 and 3) having the prefix "a." indicates organs, tissues, or cells derived from "adult" sources. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease." The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

### Description of Table 5

Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1B.1, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL:

www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B.1, column 8, as determined using the Morbid Map database.

#### Description of Table 6

[0049] Table 6 summarizes some of the ATCC™ Deposits, Deposit dates, and ATCC™ designation numbers of deposits made with the ATCC™ in connection with the present application. These deposits were made in addition to those described in the Table 1A.

#### Description of Table 7

[0050] Table 7 shows the cDNA libraries sequenced, and ATCC™ designation numbers and vector information relating to these cDNA libraries.

[0051] The first column shows the first four letters indicating the Library from which each library clone was derived. The second column indicates the catalogued tissue description for the corresponding libraries. The third column indicates the vector containing the corresponding clones. The fourth column shows the  $ATCC^{TM}$  deposit designation for each library clone as indicated by the deposit information in Table 6.

### Definitions

[0052] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

10053] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

100541 In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

10055] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof (e.g., the polypeptide delinated in columns fourteen and fifteen of Table 1A); a nucleic acid sequence contained in SEQ ID NO:X (as described in column 5 of Table 1B) or the complement thereof; a cDNA sequence contained in Clone ID: (as described in column 2 of Table 1A and/or Table 1B and contained within a library deposited with the ATCC<sup>TM</sup>); a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 (EXON From-To) of Table 1C or a fragment or variant thereof, or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complement thereof. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[0056] In the present invention, "SEO ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEO ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1B, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID:). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Table 7 provides a list of the deposited cDNA libraries. One can use the Clone ID: to determine the library source by reference to Tables 6 and 7. Table 7 lists the deposited cDNA libraries by name and links each library to an ATCC™ Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone (Clone ID) isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1A and/or Table 1B correlates the Clone ID names with SEQ ID NO:X. Thus, starting with an SEQ ID NO:X, one can use Tables 1A, 1B, 6, 7, and 9 to determine the corresponding Clone ID, which library it came from and which ATCCTM deposit the library is contained in, Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC™ is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCCTM denosits were made pursuant to the terms of the Budanest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

In specific embodiments, the polymucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polymucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polymucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5° or 3° to the gene of interest in the genome). In other embodiments, the polymucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0088] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 7 and 8 of Table 1A or the complement thereof, the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID: (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of cDNA clones deposited with the ATCCT<sup>M</sup>, described herein), and/or the polynucleotide sequence delineated in column 6 of Table 1C or the complement thereof. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[0059] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCI; 0.2M NaHzPO4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.11% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[9060] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhard's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility. [9061] Of course, a polymucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a CDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polymucleotide," since such a polymucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement therrof (e.g., practically any

double-stranded cDNA clone generated using oligo dT as a primer).

100621 The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, ingle- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single- stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[1003] In specific embodiments, the polymucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 100 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polymucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polymucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polymucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO.X" refers to a polymucleotide sequence described in column 5 of Table 1A, while 
"SEQ ID NO.Y" refers to a polypeptide sequence described in column 10 of Table 1A. SEQ ID NO.X is 
identified by an integer specified in column 6 of Table 1A. The polypeptide sequence SEQ ID NO.X is a 
translated open reading frame (ORF) encoded by polymucleotide SEQ ID NO.X. The polypucleotide 
sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, 
a polypeptide sequence corresponding to polymucleotide sequence SEQ ID NO.2 is the first polypeptide 
sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide 
sequence shown as SEO ID NO.3 and so on.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS -STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

"SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1A, Table 1B, or Table 2, while "SEQ ID NO:X" refers to a polypeptide sequence described in column 11 of Table 1A and or of Table 1B. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1B. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID:" refers to a cDNA clone described in column 2 of Table 1A and/or 1B.

"A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity (e.g. activity useful in treating, preventing and/or ameliorating diabetes mellitus), antigenicity (ability to bind [or compete with a polypeptide for binding] to an anti-polypeptide antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[10083] The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Specifically, one of skill in the art may routinely assay secreted polypeptides (including fragments and variants) of the invention for activity using assays as described in the examples section below.

"A polypeptide having biological activity" refers to a polypeptide extibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency dose sexist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

# TABLES

### Table 1A

[0070] Table 1A summarizes information concerning certain polypnucleotides and polypeptides of the invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCCTM Deposit No: Z and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column, the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh column) and the "3' NT of Clone Seq." (eighth column) of SEO ID NO:X. In the ninth column, the nucleotide position of SEO ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon," Similarly, in column ten, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep." In the eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEO ID NO:Y." although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

100711 In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEO ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEO ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF". 100721 SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEO ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEO ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1A

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

and/or elsewhere herein

[10074] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC™, as set forth in Table 1A. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

10075] The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

[0076] Also provided in Table I.A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

[0077] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Nucleic 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037, pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene.

Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into E. coli strain XL-1 Blue, also available from Stratasene

[4078] Vectors pSport1, p.CMVSport 1.0, p.CMVSport 2.0 and p.CMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., Focus 15:59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL1-1 Blue. Vector pCR\*2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., BioTechnology 9: (1991).

100791 The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding ener from amorporists sources of genomic material.

[0080] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences disclosed herein or the clones deposited with the ATCC™. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

10081] The present invention provides a polymuclocide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC™ Deposit No.Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC™ Deposit No.Z. Polymuclotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA contained in ATCC™ Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynuclocide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC™ Deposit No.Z.

Table 1A Table 1A

|      | TADIC IA |              |             |     |       |       |       |          |          |     |       |      |          |       |
|------|----------|--------------|-------------|-----|-------|-------|-------|----------|----------|-----|-------|------|----------|-------|
|      |          |              |             | IN  |       |       |       |          | 2, N.L   | AA  | First | Last |          |       |
|      |          | ATCCTM       |             | SEO |       | 5' NT | 3, NT |          | of First | SEO | ΑĄ    | ΑĄ   | First AA | Last  |
|      |          | Deposit No:Z |             | É   | Total | Jo    | jo    | 5' NT    | AA of    | É   | jo    | jo   | Jo       | AA of |
| Gene | cDNA     | and Date     |             | ÖN  | K     | Clone | Clone | of Start | Signal   | ÖN  | Sig   | Sig  | Secreted | ORF   |
| No.  | Clone ID |              | Vector      | ×   | Seq.  | Seq.  | Seq.  |          | Pep      | Y   | Pep   | Pep  | Portion  |       |
| _    | H2CBU83  | 209889       | pBluescript | 11  | 2703  | 1     | 2703  | 157      | 157      |     | -     | 30   | 31       | 202   |
|      |          | 05/22/98     | SK-         |     |       |       |       |          |          | 405 |       |      |          |       |
| -    | H2CBU83  | 209889       | pBluescript |     | 2709  | 1     | 2709  | 157      | 157      |     | _     | 30   | 31       | 51    |
|      |          | 05/22/98     | SK-         | 262 |       |       |       |          |          | 959 |       |      |          |       |
| 2    | H6EDC19  | 209324       | Uni-ZAP XR  | 12  | 092   | 324   | 092   | 389      | 389      |     | 1     | 25   | 26       | 114   |
|      |          | 10/02/97     |             |     |       |       |       |          |          | 406 |       |      |          |       |
| 3    | HACBD91  | 209626       | Uni-ZAP XR  | 13  | 1445  | 1     | 1445  | 111      | 117      |     | 1     | 42   | 43       | 49    |
|      |          | 02/12/98     |             |     |       |       |       |          |          | 407 |       |      |          |       |
| 4    | HACCI17  | 203071       | Uni-ZAP XR  | 14  | 1722  | 336   | 1714  | 461      | 194      |     | _     | 24   | 25       | 218   |
|      |          | 07/27/98     |             |     |       |       |       |          |          | 408 |       |      |          |       |
| 4    | HACCI17  | 203071       | Uni-ZAP XR  |     | 1380  | 12    | 1380  | 135      | 135      |     | -     | 24   | 25       | 72    |
|      |          | 07/27/98     |             | 263 |       |       |       |          |          | 657 |       |      |          |       |
| 5    | HAGAQ26  | 209368       | Uni-ZAP XR  | 51  | 1333  | 157   | 1333  | 251      | 251      |     | 1     | 20   | 21       | 62    |
|      |          | 10/16/97     |             |     |       |       |       |          |          | 409 |       |      |          |       |
| 9    | HAGDS35  | 209299       | Uni-ZAP XR  | 91  | 121   | 1     | 751   | 45       | 45       |     | 1     | 23   | 24       | 122   |
|      |          | 09/25/97     |             |     |       |       |       |          |          | 410 |       |      |          |       |
| 9    | HAGDS35  | 209299       | Uni-ZAP XR  |     | 813   | 1     | 813   | 52       | 52       |     | 1     | 23   | 24       | 811   |
|      |          | 09/25/97     |             | 264 |       |       |       |          |          | 859 |       |      |          |       |
| 7    | HAGFI62  | 209782       | Uni-ZAP XR  | 41  | 1003  | 368   | 992   | 429      | 459      |     | 1     | 28   | 59       | 16    |
|      |          | 04/20/98     |             |     |       |       |       |          |          | 411 |       |      |          |       |
| 8    | HAHDB16  | 209626       | Uni-ZAP XR  | 18  | 962   | 1     | 962   | 93       | 93       |     | -     | 20   | 21       | 50    |
|      |          | 02/12/98     |             |     |       |       |       |          |          | 412 |       |      |          |       |
| 6    | HAICP19  | 209009       | Uni-ZAP XR  | 19  | 1624  | 68    | 1483  | 128      | 128      |     | _     | 18   | 19       | 446   |
|      |          | 04/28/97     |             |     |       |       |       |          |          | 413 |       |      |          |       |

|                            |                     |            |                     | _                   |                    |                  |                  | _                  |                    |                    |                    |            |                 |                 |                    |
|----------------------------|---------------------|------------|---------------------|---------------------|--------------------|------------------|------------------|--------------------|--------------------|--------------------|--------------------|------------|-----------------|-----------------|--------------------|
| Last<br>AA of              | ORF                 | 140        | 563                 | 169                 | 53                 | 421              | 47               | 242                | 203                | 4                  | 20                 | 189        | 123             | 140             | 49                 |
| First AA<br>of             | Secreted<br>Portion | 30         | 16                  | 16                  | 20                 | 35               | 24               | 19                 | 19                 | 59                 | 30                 | 23         | 7               | 56              | 17                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 29         | 15                  | 15                  | 19                 | 34               | 23               | 18                 | 18                 | 28                 | 29                 | 22         | -               | 25              | 16                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1          | -                   | -                   | 1                  | 1                | 1                | -                  | 1                  | 1                  | 1                  | 1          | -               | -               | 1                  |
| AA<br>SEQ                  | NO:<br>Y            | 414        | 415                 | 629                 | 416                | 417              | 099              | 418                | 199                | 419                | 420                | 421        | 662             | 422             | 423                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 274        | 109                 | 120                 | 262                | 1495             | 226              | 86                 | 40                 | 252                | 94                 | 251        | 448             | 385             | 252                |
| 5' NT                      | of Start<br>Codon   | 274        | 109                 | 120                 | 262                | 1495             | 226              | 86                 | 40                 | 252                | 94                 | 251        | 448             | 385             | 252                |
| 3' NT<br>of                | Clone<br>Seq.       | 628        | 2849                | 2288                | 755                | 4129             | 3758             | 1674               | 1534               | 1479               | 742                | 2005       | 2664            | 1153            | 812                |
| S' NT<br>of                | Clone<br>Seq.       | 1          | -                   | -                   | 1                  | -                | 1                | 47                 | -                  | 45                 | 1                  | 1          | -               | -               | 1                  |
| Total                      | NT<br>Seq.          | 879        | 2849                | 2288                | 755                | 4129             | 3758             | 1674               | 1534               | 1503               | 742                | 2005       | 2664            | 1153            | 812                |
| SEQ                        | X.                  | 20         | 21                  | 265                 | 22                 | 23               | 266              | 24                 | 267                | 25                 | 26                 | 27         | 268             | 28              | 29                 |
|                            | Vector              | Uni-ZAP XR | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pCMVSport<br>3.0   | pCMVSport<br>3.0 | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pCMVSport<br>3.0   | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR      | Uni-ZAP XR      | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z     | and Date            | 209852     | PTA-322<br>07/09/99 | PTA-322<br>07/09/99 | 209626<br>02/12/98 | 203364           | 203364           | 209965<br>06/11/98 | 209965<br>06/11/98 | 209651<br>03/04/98 | 209889<br>05/22/98 | 209878     | 209878 05/18/98 | 203570 01/11/99 | 209626<br>02/12/98 |
|                            | cDNA<br>Clone ID    | HAIFL18    | HAJAN23             | HAJAN23             | HAJBR69            | HAMFE15          | HAMFE15          | HAMGR28            | HAMGR28            | HAPBS03            | HAPNY94            | HAPOM49    | HAPOM49         | HAPUC89         | HATBR65            |
|                            | Gene<br>No.         | 10         | Ξ                   | Ξ                   | 12                 | 13               | 13               | 41                 | 14                 | 15                 | 16                 | 17         | 17              | 81              | 19                 |

| # 6                     | 12                  | 1                  |                    |                    | _          |                 | <sub>10</sub>        | -<br>-               | _                    | Г                  | I                   | <u></u>             | _                   | Γ          |                    |
|-------------------------|---------------------|--------------------|--------------------|--------------------|------------|-----------------|----------------------|----------------------|----------------------|--------------------|---------------------|---------------------|---------------------|------------|--------------------|
| Last                    | ORF                 | 49                 | 23                 | 59                 | 240        | 09              | 185                  | 178                  | 219                  | 39                 | 174                 | 173                 | 210                 | 40         | 46                 |
| First AA                | Secreted<br>Portion | 61                 | Ξ                  | 20                 | 39         | 39              | 22                   | 22                   | 7                    | 61                 | 31                  | 30                  | 30                  | 40         | 35                 |
| Last<br>AA              | Sig<br>Pep          | 81                 | 01                 | 61                 | 38         | 38              | 21                   | 21                   | -                    | 81                 | 30                  | 59                  | 59                  | 39         | 34                 |
| First<br>AA<br>of       | Sig<br>Pep          | -                  | -                  | _                  | -          | -               | -                    | -                    | -                    | -                  | -                   | -                   | -                   | -          | 1                  |
| SEQ                     | S >                 | 424                | 699                | 425                | 426        | 664             | 427                  | 999                  | 999                  | 428                | 429                 | 199                 | 899                 | 430        | 431                |
| 5' NT<br>of First       | Signal<br>Pep       | 253                | 575                | 390                | 124        | 62              | 125                  | 62                   | 7                    | 75                 | 57                  | 71                  | 100                 | 20         | 87                 |
| TN 'S                   | of Start<br>Codon   | 253                |                    | 390                | 124        | 62              | 125                  | 79                   |                      | 75                 | 57                  | 71                  | 100                 | 20         | 87                 |
| 3'NT<br>of              | Clone<br>Seq.       | 988                | 1076               | 821                | 186        | 933             | 864                  | 941                  | 853                  | 1038               | 843                 | 1566                | 1067                | 849        | 872                |
| S' NT                   | Clone<br>Seq.       | 1                  | -                  | 330                | 1          | -               | -                    | _                    | 804                  | -                  | -                   | -                   | -                   | -          | 1                  |
| Total                   | Seq.                | 910                | 1076               | 821                | 186        | 943             | 864                  | 941                  | 886                  | 1038               | 843                 | 1566                | 1067                | 849        | 872                |
| SEQ                     | ÿ×                  | 30                 | 269                | 31                 | 32         | 270             | 33                   | 271                  | 272                  | 34                 | 35                  | 273                 | 274                 | 36         | 37                 |
|                         | Vector              | Uni-ZAP XR         | Uni-ZAP XR         | pSport1            | Uni-ZAP XR | Uni-ZAP XR      | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR         | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pCMVSport<br>3.0    | Uni-ZAP XR | Uni-ZAP XR         |
| ATCCTM<br>Denosit No: 2 | and Date            | 209626<br>02/12/98 | 209626<br>02/12/98 | 209683<br>03/20/98 | 209878     | 209878 05/18/98 | PTA-2073<br>06/09/00 | PTA-2073<br>06/09/00 | PTA-2073<br>06/09/00 | 209224<br>08/28/97 | PTA-885<br>10/28/99 | PTA-885<br>10/28/99 | PTA-885<br>10/28/99 | 209125     | 209651<br>03/04/98 |
|                         | cDNA<br>Clone ID    | HAUAI83            | HAUAI83            | HBAMB15            | HBGBA69    | HBGBA69         | HBGNU56              | HBGNU56              | HBGNU56              | HBIAE26            | HBINS58             | HBINS58             | HBINS58             | HBJFU48    | HBJLC01            |
|                         | Gene<br>No.         | 20                 | 20                 | 21                 | 22         | 22              | 23                   | 23                   | 23                   | 24                 | 25                  | 25                  | 25                  | 76         | 27                 |

| -                                  |          |                    |            |                    |                    |            |                      |                      |                    |            |                    |                    |                     |                     |                     |
|------------------------------------|----------|--------------------|------------|--------------------|--------------------|------------|----------------------|----------------------|--------------------|------------|--------------------|--------------------|---------------------|---------------------|---------------------|
| Last<br>AA of<br>ORF               |          | 19                 | 319        | 336                | 501                | 272        | 68                   | 68                   | 25                 | 15         | 63                 | 74                 | 127                 | 127                 | 6                   |
| First AA<br>of<br>Secreted         | Portion  | 38                 | 20         | 20                 | 20                 | 21         | 36                   | 36                   | 29                 | 61         | 21                 | 31                 | 25                  | 84                  | 6                   |
| Last<br>AA<br>of<br>Sig            | Pep      | 37                 | 61         | 61                 | 61                 | 20         | 35                   | 35                   | 28                 | 81         | 20                 | 30                 | 24                  | 47                  | 8                   |
| First<br>AA<br>of<br>Sig           | Pep      | 1                  | -          | -                  | 1                  | 1          | 1                    | 1                    | 1                  | 1          | 1                  | 1                  | -                   | -                   | 1                   |
| SEQ B SEQ                          | ٨        | 432                | 433        | 434                | 699                | 435        | 436                  | 029                  | 437                | 438        | 439                | 440                | 4                   | 671                 | 672                 |
| N 2 4 W                            |          | 77                 | 991        | 165                | 165                | 113        | 12                   | 5                    | 10                 | 991        | 28                 | 438                | 21                  | 124                 | 603                 |
| 5' NT<br>of Start                  | Codon    | 77                 | 166        | 165                | 591                | 113        | 12                   | 5                    | 10                 | 166        | 28                 | 438                | 21                  | 124                 |                     |
| f . 40                             |          | 109                | 1256       | 2084               | 2078               | 1765       | 2494                 | 2451                 | 1509               | 885        | 639                | 780                | 1343                | 845                 | 738                 |
| 5° NT<br>of<br>Clone               | Seq.     | 1                  | 61         | -                  | 1                  | 1          | -                    | -                    | -                  | 13         | 1                  | -                  | -                   | -                   | 1                   |
| Total<br>NT                        | Seq.     | 109                | 1276       | 2084               | 2078               | 1765       | 2494                 | 2494                 | 1509               | 885        | 639                | 790                | 1343                | 845                 | 738                 |
| SEQ<br>NO:                         | ×        | 38                 | 39         | 40                 | 275                | 41         | 42                   | 276                  | 43                 | 4          | 45                 | 46                 | 47                  | 277                 | 278                 |
|                                    | Vector   | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR         | Uni-ZAP XR | pSport1            | pCMVSport<br>2.0   | Lambda ZAP<br>II    | Lambda ZAP<br>II    | Lambda ZAP<br>II    |
| ATCCTM<br>Deposit No:Z<br>and Date |          | 209242<br>09/12/97 | 209626     | 209878<br>05/18/98 | 209878<br>05/18/98 | 209580     | PTA-2069<br>06/09/00 | PTA-2069<br>06/09/00 | 209651<br>03/04/98 | 209300     | 209324<br>10/02/97 | 209627<br>02/12/98 | PTA-855<br>10/18/99 | PTA-855<br>10/18/99 | PTA-855<br>10/18/99 |
| cDNA                               | Clone ID | HBNAW17            | HCE2F54    | HCE3G69            | HCE3G69            | HCE5F43    | HCEFB80              | HCEFB80              | HCENK38            | HCEWE20    | HCFOM18            | HCGMD59            | HCNDR47             | HCNDR47             | HCNDR47             |
| Gene                               | No.      | 28                 | 59         | 30                 | 30                 | 31         | 32                   | 32                   | 33                 | 34         | 35                 | 36                 | 37                  | 37                  | 37                  |

| Last<br>AA of              | ORF                 | 43                 | 61                  | 7                   | 44                   | 47                 | 001                | 40                 | 45                 | 146                | 146             | 941                 | 941                 | 316              | 271                |
|----------------------------|---------------------|--------------------|---------------------|---------------------|----------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-----------------|---------------------|---------------------|------------------|--------------------|
| First AA<br>of             | Secreted<br>Portion | 22                 |                     |                     | 25                   | 28                 | 81                 | 61                 | 31                 | 30                 | 30              | 33                  | 33                  | 316              | 31                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 21                 |                     |                     | 24                   | 27                 | 17                 | 18                 | 30                 | 59                 | 59              | 32                  | 32                  | 315              | 30                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1                  | 1                   | -                   | 1                    | 1                  | 1                  | -                  | 1                  | 1                  | 1               | 1                   | -                   | 1                | 1                  |
| SEQ<br>ID                  | ΝΘ:<br>Υ            | 442                | 443                 | 673                 | 444                  | 445                | 446                | 447                | 448                | 449                | 674             | 450                 | 675                 | 451              | 676                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 218                | 381                 | 1702                | 16                   | 557                | 61                 | 37                 | 270                | 33                 | 28              | 259                 | 69                  | 37               | 103                |
| 5' NT                      | of Start<br>Codon   | 218                |                     |                     | 16                   | 557                | 61                 | 37                 | 270                | 33                 | 28              | 259                 | 69                  | 37               | 103                |
| 3' NT<br>of                | Clone<br>Seq.       | 712                | 629                 | 2333                | 627                  | 736                | 320                | 710                | 1428               | 1691               | 1746            | 3447                | 4909                | 1513             | 1184               |
| 5° NT<br>of                | Clone<br>Seq.       | 1                  | 1                   | 1324                | 1                    | 331                | 1                  | -                  | 208                | 1                  | 1               | 197                 | -                   | -                | 598                |
| Total                      | Seq.                | 712                | 629                 | 2333                | 627                  | 875                | 320                | 710                | 1428               | 1691               | 1746            | 3447                | 4906                | 1513             | 1579               |
| SEQ                        | ÿ×                  | 48                 | 49                  | 279                 | 50                   | 51                 | 52                 | 53                 | 54                 | 22                 | 280             | 99                  | 281                 | 57               | 282                |
|                            | Vector              | pBluescript        | Lambda ZAP<br>II    | Lambda ZAP<br>II    | ZAP Express          | ZAP Express        | ZAP Express        | ZAP Express        | ZAP Express        | pSport1            | pSport1         | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pCMVSport<br>3.0 | pCMVSport<br>3.0   |
| ATCCTM<br>Deposit No:Z     | and Date            | 209242<br>09/12/97 | PTA-884<br>10/28/99 | PTA-884<br>10/28/99 | PTA-1544<br>03/21/00 | 209324<br>10/02/97 | 209852<br>05/07/98 | 209324<br>10/02/97 | 209627<br>02/12/98 | 209965<br>06/11/98 | 209965 06/11/98 | PTA-163<br>06/01/99 | PTA-163<br>06/01/99 | 209853 05/07/98  | 209853<br>05/07/98 |
|                            | cDNA<br>Clone ID    | HCNSB61            | нсост05             | нсост05             | HCUGM86              | HCUIM65            | HCWDS72            | HCWKC15            | HCWUM50            | HDABR72            | HDABR72         | HDPBA28             | HDPBA28             | HDPB132          | HDPB132            |
|                            | Gene<br>No.         | 38                 | 39                  | 39                  | 40                   | 14                 | 42                 | 43                 | 44                 | 45                 | 45              | 46                  | 46                  | 47               | 47                 |

| -                                        |          |                  |                    |                      |                      | _                    | _                  |                    |                    | _                  | _                  |                  |                  |                     |                     |
|------------------------------------------|----------|------------------|--------------------|----------------------|----------------------|----------------------|--------------------|--------------------|--------------------|--------------------|--------------------|------------------|------------------|---------------------|---------------------|
| Last<br>AA of<br>ORF                     |          | 138              | 51                 | 267                  | 157                  | 118                  | 23                 | 87                 | 40                 | 525                | 59                 | 484              | 122              | 46                  | 46                  |
| First AA<br>of<br>Secreted               | Portion  | 36               | 59                 | 59                   | 18                   | 7                    | 21                 | 29                 | 31                 | 09                 | 21                 | 23               | 61               | 33                  | 27                  |
| Last<br>AA<br>of<br>Sig                  | Pep      | 35               | 28                 | 58                   | 17                   | 9                    | 20                 | 28                 | 30                 | 59                 | 20                 | 22               | 18               | 32                  | 26                  |
| First<br>AA<br>of<br>Sig                 | Pep      | 1                | -                  | -                    | 1                    | 1                    | 1                  | -                  | 1                  | 1                  | 1                  | 1                | -                | -                   | 1                   |
| SEQ<br>NO. B.                            | Y        | 229              | 452                | 453                  | 878                  | 629                  | 454                | 455                | 456                | 457                | 089                | 458              | 459              | 460                 | 681                 |
| 5' NT<br>of First<br>AA of<br>Signal     | Pep      | 51               | 131                | 35                   | 260                  | 909                  | 182                | ∞                  | 245                | 59                 | 259                | 15               | 159              | 127                 | 117                 |
| 5' NT<br>of Start                        | Codon    | 51               | 131                | 35                   | 260                  |                      | 182                | ∞                  | 245                | 59                 | 259                | 15               | 159              | 127                 | 117                 |
| 3' NT<br>of<br>Clone                     | Seq.     | 287              | 6107               | 3037                 | 2921                 | 1259                 | 792                | 2687               | 728                | 1633               | 1313               | 1727             | 1655             | 6297                | 2042                |
| 5° NT<br>of<br>Clone                     | Seq.     | 1                | -                  | 115                  | 1                    | 358                  | 76                 | 138                | 1                  | 308                | 1                  | 1                | -                | -                   | 1                   |
| Total<br>NT                              | Seq.     | 587              | 6107               | 3037                 | 2921                 | 1259                 | 192                | 2687               | 728                | 1635               | 1314               | 1727             | 1655             | 6297                | 2042                |
| SEQ<br>ID<br>NO:                         | Х        | 283              | 28                 | 65                   | 284                  | 285                  | 99                 | 19                 | 62                 | 63                 | 286                | 49               | 9                | 99                  | 287                 |
|                                          | Vector   | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pCMVSport<br>3.0     | pCMVSport<br>3.0     | pCMVSport<br>3.0     | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0 | pCMVSport<br>3.0 | pCMVSport<br>3.0    | pCMVSport<br>3.0    |
| ATCC <sup>TM</sup> Deposit No:Z and Date |          | 209853           | 209877<br>05/18/98 | PTA-1544<br>03/21/00 | PTA-1544<br>03/21/00 | PTA-1544<br>03/21/00 | 209125<br>06/19/97 | 203027<br>06/26/98 | 209125<br>06/19/97 | 209563<br>12/18/97 | 209563<br>12/18/97 | 209627           | 209878 05/18/98  | PTA-867<br>10/26/99 | PTA-867<br>10/26/99 |
| cDNA                                     | Clone ID | HDPB132          | HDPCJ91            | HDPCL63              | HDPCL63              | HDPCL63              | HDPC025            | HDPGT01            | HDPHI51            | HDPJM30            | HDPJM30            | HDPND46          | HDPOJ08          | HDPPN86             | HDPPN86             |
| Gene                                     | No.      | 47               | 84                 | 49                   | 46                   | 46                   | 20                 | 51                 | 52                 | 53                 | 53                 | 54               | 55               | 99                  | 99                  |

| 5                                           | 1                   |                     |                     |                     | _                   |                     | _                   |                    |                    |                    |                    | _                   | ı —              |                    |
|---------------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|---------------------|------------------|--------------------|
| Last<br>AA of<br>ORF                        | 99                  | 4                   | 4                   | 107                 | 6                   | 127                 | 8                   | 710                | 308                | 48                 | 22                 | 549                 | 467              | 325                |
| First AA<br>of<br>Secreted<br>Portion       | 61                  | 81                  | ∞                   | 2                   | 50                  | 20                  | 20                  | 21                 | 21                 | 61                 | 42                 | 61                  | 61               | 24                 |
| Last<br>AA<br>of<br>Sig<br>Pep              | 81                  | 17                  | 7                   | _                   | 61                  | 61                  | 61                  | 20                 | 20                 | 81                 | 4                  | 81                  | 81               | 23                 |
| First<br>AA<br>of<br>Sig<br>Pep             | -                   | -                   | -                   | -                   | -                   | -                   | -                   | -                  | -                  | -                  | -                  | -                   | -                | -                  |
| AA<br>SEQ<br>NÖ:                            | 461                 | 682                 | 683                 | 684                 | 462                 | 685                 | 989                 | 463                | 687                | 464                | 889                | 465                 | 466              | 467                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 123                 | 116                 | 1525                | 345                 | 158                 | 153                 | 212                 | 184                | 227                | 2356               | 179                | 06                  | 40               | 117                |
| 5' NT<br>of Start<br>Codon                  | 123                 |                     |                     |                     | 158                 | 153                 | 212                 | 184                | 227                | 2356               | 6/1                | 06                  | 40               | 117                |
| 3° NT<br>of<br>Clone<br>Seq.                | 3408                | 308                 | 1568                | 865                 | 1663                | 1687                | 570                 | 2343               | 1752               | 3091               | 536                | 2916                | 1748             | 1277               |
| 5' NT<br>of<br>Clone<br>Seq.                | 1                   | -                   | 1                   | 1                   | 1                   | 1                   | -                   | 1                  | 1                  | 2304               | 1                  | -                   | -                | 860                |
| Total<br>NT<br>Seq.                         | 3408                | 308                 | 1568                | 865                 | 1663                | 1687                | 570                 | 2343               | 1752               | 3091               | 536                | 2916                | 1748             | 1277               |
| SEQ NI<br>NO ID                             | 29                  | 288                 | 289                 | 290                 | 89                  | 291                 | 292                 | 69                 | 293                | 70                 | 294                | 71                  | 72               | 73                 |
| Vector                                      | pCMVSport<br>3.0    | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0    | pCMVSport<br>3.0 | pCMVSport<br>3.0   |
| ATCCTM Deposit No:Z and Date                | PTA-868<br>10/26/99 | 209745<br>04/07/98 | 209745<br>04/07/98 | 209782<br>04/20/98 | 209782<br>04/20/98 | PTA-163<br>06/01/99 | 203331           | 209782<br>04/20/98 |
| cDNA<br>Clone ID                            | HDPSB18             | HDPSB18             | HDPSB18             | HDPSB18             | HDPSH53             | HDPSH53             | HDPSH53             | HDPSP01            | HDPSP01            | HDPSP54            | HDPSP54            | HDPUH26             | HDPUW68          | HDPWU34            |
| Gene<br>No.                                 | 57                  | 57                  | 57                  | 57                  | 28                  | 28                  | 28                  | 65                 | 65                 | 09                 | 09                 | 19                  | 62               | 63                 |

|                            |                     | _         |                     |                     |                     |                     |                    |                    |                    |                    |                                         |                                         |                    | ,                  |
|----------------------------|---------------------|-----------|---------------------|---------------------|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|-----------------------------------------|-----------------------------------------|--------------------|--------------------|
| Last<br>AA of              | Ş                   | 44        | 86                  | 86                  | 22                  | 25                  | 809                | 95                 | 108                | 73                 | 540                                     | 81                                      | 66                 | 99                 |
| First AA                   | Secreted<br>Portion | 17        | 38                  | 38                  | 01                  | 17                  | 23                 | 21                 | 21                 | 21                 | 31                                      | 23                                      | 37                 | 22                 |
| Last<br>of<br>of           | Sig<br>Pep          | 91        | 37                  | 37                  | 6                   | 16                  | 22                 | 20                 | 20                 | 20                 | 30                                      | 22                                      | 36                 | 21                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1         | -                   | _                   | -                   | -                   | -                  | -                  | -                  | -                  | -                                       | _                                       | -                  | 1                  |
| SEQ                        | N<br>N              | 067       | 468                 | 069                 | 169                 | 692                 | 469                | 470                | 693                | 694                | 471                                     | 695                                     | 472                | 473                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 111       | 23                  | 33                  | 539                 | 1190                | 326                | 132                | 148                | 148                | 808                                     | 515                                     | 66                 | 28                 |
| 5' NT                      | or Start<br>Codon   | 111       | 23                  | 33                  |                     |                     | 326                | 132                | 148                | 148                | 808                                     | 515                                     | 66                 | 28                 |
| 3°NT<br>of                 | Clone<br>Seq.       | 427       | 992                 | 2409                | 423                 | 1471                | 2181               | 2207               | 2206               | 2206               | 3532                                    | 1115                                    | 867                | 1558               |
| S, NT                      | Clone<br>Seq.       | 1         | -                   | -                   | -                   | 105                 | -                  | -                  | 1                  | -                  | 2821                                    | 435                                     | -                  | -                  |
| Total                      | Seq                 | 427       | 992                 | 2409                | 737                 | 1471                | 2181               | 2207               | 2227               | 2214               | 3533                                    | 1145                                    | 867                | 1558               |
| SE SE                      | ğχ                  | 306       | 74                  | 296                 | 297                 | 298                 | 75                 | 92                 | 299                | 300                | 77                                      | 301                                     | 78                 | 79                 |
|                            | Vector              | pCMVSport | pCMVSport           | pCMVSport           | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pCMVSport<br>2.0   | pCMVSport<br>2.0   | pCMVSport<br>2.0   | pCMVSport<br>2.0   | Uni-ZAP XR                              | Uni-ZAP XR                              | Uni-ZAP XR         | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z     | and Date            | 209782    | PTA-868<br>10/26/99 | PTA-868<br>10/26/99 | PTA-868<br>10/26/99 | PTA-868<br>10/26/99 | 203070<br>07/27/98 | 209965<br>06/11/98 | 209965<br>06/11/98 | 209965<br>06/11/98 | 97923<br>03/07/97<br>209071<br>05/22/97 | 97923<br>03/07/97<br>209071<br>05/22/97 | 209877<br>05/18/98 | 209603<br>01/29/98 |
| 16                         | Clone ID            | HDPWU34   | HDPXY01             | HDPXY01             | HDPXY01             | HDPXY01             | HDTBV77            | ното023            | ното023            | ното 23            | HE2DE47                                 | HE2DE47                                 | HE2NV57            | HE2PH36            |
|                            | No.                 | £9        | 49                  | 4                   | 49                  | 45                  | 9                  | 99                 | 99                 | 99                 | 29                                      | 29                                      | 89                 | 69                 |

| Last<br>AA of<br>ORF                        | 72                   | 41                 | 41                                       | 355                | 313                | 134                | 46                 | 47      | 121                | 122                | 87                   | 116                | 98                 |
|---------------------------------------------|----------------------|--------------------|------------------------------------------|--------------------|--------------------|--------------------|--------------------|---------|--------------------|--------------------|----------------------|--------------------|--------------------|
| First AA<br>of<br>Secreted<br>Portion       | 25                   | 27                 | 27                                       | 34                 | 31                 | 31                 | 61                 | 24      | 29                 | 59                 | 27                   | 22                 | 43                 |
| Last<br>of<br>Sig<br>Pep                    | 24                   | 26                 | 26                                       | 33                 | 30                 | 30                 | 18                 | 23      | 28                 | 28                 | 56                   | 21                 | 42                 |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                    | 1                  | -                                        | 1                  | 1                  | 1                  | 1                  | 1       | 1                  | 1                  | 1                    | 1                  | 1                  |
| A SEQ A                                     | 474                  | 475                | 476                                      | 477                | 969                | 697                | 478                | 479     | 480                | 869                | 481                  | 482                | 483                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 16                   | 191                | 35                                       | 129                | 136                | 129                | 57                 | 123     | 73                 | -67                | 53                   | 199                | 232                |
| 5' NT<br>of Start<br>Codon                  | 16                   | 191                | 35                                       | 129                | 136                | 129                | 57                 | 123     | 73                 | -67                | 53                   | 199                | 232                |
| 3° NT<br>of<br>Clone<br>Seq.                | 2199                 | 1077               | 832                                      | 1209               | 1165               | 1160               | 1280               | 1336    | 799                | 802                | 1345                 | 1347               | 642                |
| of<br>Clone<br>Seq.                         | 1                    | -                  | -                                        | -                  | -                  | -                  | 25                 | 1       | -                  | 1                  | -                    | 1                  | 1                  |
| Total<br>NT<br>Seq.                         | 2199                 | 1077               | 832                                      | 1209               | 1165               | 1160               | 1669               | 1336    | 799                | 802                | 1345                 | 1347               | 642                |
| X NO B SEQ                                  | 80                   | 81                 | 82                                       | 83                 | 302                | 303                | 84                 | 82      | 98                 | 304                | 87                   | 88                 | 89                 |
| Vector                                      | Uni-ZAP XR           | Uni-ZAP XR         | Uni-ZAP XR                               | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR         | pSport1 | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR           | Uni-ZAP XR         | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z<br>and Date          | PTA-1544<br>03/21/00 | 209551<br>12/12/97 | 209010<br>04/28/97<br>209085<br>05/29/97 | 203570<br>01/11/99 | 203570<br>01/11/99 | 203570<br>01/11/99 | 209745<br>04/07/98 | 209563  | 209423<br>10/30/97 | 209423<br>10/30/97 | PTA-1544<br>03/21/00 | 209407<br>10/23/97 | 209277<br>09/18/97 |
| cDNA<br>Clone ID                            | HE8DS15              | HE9CO69            | HE9HY07                                  | HE9OW20            | HE9OW20            | HE9OW20            | HEEAG23            | неомоез | HEPAB80            | HEPAB80            | HFABG18              | HFABH95            | HFAEF57            |
| Gene<br>No.                                 | 20                   | 17                 | 72                                       | 73                 | 73                 | 73                 | 74                 | 7.5     | 9/                 | 9/                 | 77                   | 28                 | 62                 |

| Last<br>AA of<br>ORF                        | 01                                       | 45                 | 38                 | 43                  | 43                  | 7                   | 44                 | 23                 | 34                 | 89                 | 162              | 29                 | 47                 | 28                 |
|---------------------------------------------|------------------------------------------|--------------------|--------------------|---------------------|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|------------------|--------------------|--------------------|--------------------|
| First AA<br>of<br>Secreted<br>Portion       |                                          | 81                 | 61                 | 40                  | 40                  |                     | 23                 | 61                 | 21                 | 23                 | 25               | 37                 | 61                 | 20                 |
| Last<br>AA<br>of<br>Sig<br>Pep              |                                          | 17                 | 18                 | 39                  | 39                  |                     | 22                 | 18                 | 20                 | 22                 | 24               | 36                 | 18                 | 19                 |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                                        | 1                  | 1                  | 1                   | 1                   | 1                   | 1                  | 1                  | 1                  | 1                  | 1                | 1                  | 1                  | 1                  |
| SEQ AA                                      | 484                                      | 485                | 486                | 487                 | 669                 | 700                 | 488                | 489                | 490                | 491                | 492              | 493                | 494                | 495                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 487                                      | 4                  | 1019               | 45                  | 52                  | 280                 | 50                 | 110                | 158                | 547                | 152              | 247                | 86                 | 4                  |
| 5' NT<br>of Start<br>Codon                  |                                          | 44                 | 1019               | 45                  | 52                  |                     | 20                 | 110                | 158                | 547                | 152              | 247                | 86                 | 44                 |
| 3' NT<br>of<br>Clone<br>Seq.                | 802                                      | 470                | 1861               | 1450                | 559                 | 829                 | 541                | 795                | 740                | 1103               | 1633             | 1873               | 1384               | 945                |
| of<br>Clone<br>Seq.                         | 352                                      | -                  | 772                | 1                   | -                   | -                   | 1                  | 1                  | -                  | 231                | -                | -                  | -                  | -                  |
| Total<br>NT<br>Seq.                         | 802                                      | 470                | 1881               | 1450                | 559                 | 8/9                 | 541                | 795                | 762                | 1103               | 1633             | 1873               | 1384               | 945                |
| X NO B SEQ                                  | 06                                       | 16                 | 92                 | 93                  | 305                 | 306                 | 94                 | 62                 | 96                 | -64                | 86               | 66                 | 100                | 101                |
| Vector                                      | Uni-ZAP XR                               | Lambda ZAP<br>II   | Uni-ZAP XR         | pSport1             | pSport1             | pSport1             | pSport1            | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR         | Lambda ZAP<br>II | Lambda ZAP<br>II   | Lambda ZAP<br>II   | Lambda ZAP<br>II   |
| ATCCTM Deposit No:Z and Date                | 209008<br>04/28/97<br>209084<br>05/29/97 | 209242<br>09/12/97 | 209225<br>08/28/97 | PTA-846<br>10/13/99 | PTA-846<br>10/13/99 | PTA-846<br>10/13/99 | 209277<br>09/18/97 | 209627<br>02/12/98 | 209300<br>09/25/97 | 209300<br>09/25/97 | 203071           | 209580<br>01/14/98 | 209782<br>04/20/98 | 209877<br>05/18/98 |
| cDNA<br>Clone ID                            | несев37                                  | HFFAD59            | HFGAD82            | HFIIN69             | HFIIN69             | HEIIN69             | HFIUR10            | HFKFG02            | HFTBM50            | HFTDZ36            | HFXBL33          | HFXHK73            | HFXJX44            | HFXKY27            |
| Gene<br>No.                                 | 08                                       | 81                 | 82                 | 83                  | 83                  | 83                  | 84                 | 82                 | 98                 | 87                 | 88               | 68                 | 96                 | 16                 |

| Last<br>AA of<br>ORF                 | 292        | 121        | 991                 | 991                 | 56                  | 62                 | 70                 | 20               | 901                | 112                                     | 46                 | 4                                       |
|--------------------------------------|------------|------------|---------------------|---------------------|---------------------|--------------------|--------------------|------------------|--------------------|-----------------------------------------|--------------------|-----------------------------------------|
| First AA<br>of<br>Secreted           | 17         | 29         | 27                  | 27                  | 17                  | 39                 | 14                 | 28               | 22                 | 30                                      | 29                 | 34                                      |
| Last<br>AA<br>of<br>Sig              | 91         | 28         | 26                  | 26                  | 91                  | 38                 | 13                 | 27               | 21                 | 29                                      | 28                 | 33                                      |
| First<br>AA<br>of<br>Sig             | 1          | 1          | -                   | -                   | 1                   | 1                  | -                  | 1                | 1                  | 1                                       | 1                  | -                                       |
| SEQ NO:                              | 496        | 497        | 498                 | 701                 | 702                 | 499                | 703                | 200              | 501                | 502                                     | 503                | 504                                     |
| 5' NT<br>of First<br>AA of<br>Signal | 87         | 231        | 101                 | 150                 | 1260                | 88                 | 311                | 143              | 99                 | 192                                     | 140                | 230                                     |
| 5' NT<br>of Start                    | 87         | 231        | 104                 | 150                 |                     | 88                 |                    | 143              | 99                 | 192                                     | 140                | 230                                     |
| 3' NT<br>of<br>Clone                 | .vv.       | 776        | 2895                | 1042                | 1556                | 2150               | 615                | 1155             | 2566               | 199                                     | 715                | 407                                     |
| 5' NT<br>of<br>Clone                 | -bac       | 1          | 1                   | 1                   | 171                 | 1                  | -                  | 1                | 1                  | 1                                       | 1                  | 1                                       |
| Total<br>NT                          | .xq.       | 776        | 2895                | 1042                | 1556                | 2150               | 615                | 1155             | 2566               | 199                                     | 715                | 407                                     |
| SEQ NO.                              | 102        | 103        | 104                 | 307                 | 308                 | 105                | 309                | 106              | 107                | 801                                     | 109                | 110                                     |
| Vactor                               | Uni-ZAP XR | Uni-ZAP XR | pCMVSport 1         | pCMVSport 1         | pCMVSport 1         | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0 | Uni-ZAP XR         | Uni-ZAP XR                              | Lambda ZAP<br>II   | Lambda ZAP<br>II                        |
| ATCCTM<br>Deposit No:Z<br>and Date   | 209423     | 209407     | PTA-848<br>10/13/99 | PTA-848<br>10/13/99 | PTA-848<br>10/13/99 | 209853<br>05/07/98 | 209853<br>05/07/98 | 209368           | 209627<br>02/12/98 | 97975<br>04/04/97<br>209081<br>05/29/97 | 209242<br>09/12/97 | 97899<br>02/26/97<br>209045<br>05/15/97 |
| cDNA                                 | HGBHI35    | HGLAF75    | HHBCS39             | HHBCS39             | HHBCS39             | HHEAA08            | HHEAA08            | HHENV10          | HHFFJ48            | ннгнл59                                 | HHGBO91            | HHGCG53                                 |
| Gene                                 | 92         | 93         | 94                  | 94                  | 94                  | 95                 | 95                 | 96               | 97                 | 86                                      | 66                 | 100                                     |

| Last<br>AA of<br>ORF                        | 68                                      | 11                                      | 51               | 208                | 77                 | 108                | 108                | 4                   | 130                 | 122                 | 327                | 91                 | 243              |
|---------------------------------------------|-----------------------------------------|-----------------------------------------|------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|---------------------|--------------------|--------------------|------------------|
| First AA<br>of<br>Secreted<br>Portion       | 8                                       |                                         | 91               | 28                 | 59                 | 23                 | 24                 | 78                  | 7                   | 67                  | 24                 | 30                 | 18               |
| Last<br>AA<br>of<br>Sig<br>Pep              | 22                                      |                                         | 15               | 27                 | 28                 | 22                 | 23                 | 27                  | -                   | -                   | 23                 | 29                 | 17               |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                                       | 1                                       | 1                | 1                  | 1                  | 1                  | 1                  | 1                   | 1                   | -                   | 1                  | 1                  | 1                |
| AA SEQ Y                                    | 505                                     | 704                                     | 909              | 507                | 508                | 509                | 705                | 510                 | 90/                 | 707                 | 511                | 512                | 513              |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 270                                     | 270                                     | 62               | 183                | 74                 | 99                 | 47                 | 291                 | 20                  | 350                 | 232                | 09                 | 77               |
| 5' NT<br>of Start<br>Codon                  | 270                                     | 270                                     | 62               | 183                | 74                 | 99                 | 47                 | 291                 |                     |                     | 232                | 09                 | 77               |
| 3' NT<br>of<br>Clone<br>Seq.                | 711                                     | 711                                     | 875              | 2152               | 1555               | 575                | 553                | 1532                | 1614                | 1087                | 1272               | 1231               | 1189             |
| of<br>Clone<br>Seq.                         | ∞                                       | 8                                       | 1                | 141                | -                  | -                  | -                  | -                   | 1020                | 491                 | 93                 | -                  | 1                |
| Total<br>NT<br>Seq.                         | 711                                     | 711                                     | 875              | 2152               | 1555               | 575                | 553                | 1532                | 1614                | 1087                | 1559               | 1231               | 1189             |
| X NO EQ                                     | Ш                                       | 310                                     | 112              | 113                | 114                | 115                | 311                | 116                 | 312                 | 313                 | 117                | 118                | 119              |
| Vector                                      | Lambda ZAP<br>II                        | Lambda ZAP<br>II                        | Lambda ZAP<br>II | Uni-ZAP XR         | pBluescript<br>SK- | pBluescript<br>SK- | pBluescript<br>SK- | pBluescript<br>SK-  | pBluescript<br>SK-  | pBluescript<br>SK-  | pBluescript<br>SK- | Uni-ZAP XR         | pCMVSport<br>2.0 |
| ATCCTM Deposit No:Z and Date                | 97958<br>03/13/97<br>209072<br>05/22/97 | 97958<br>03/13/97<br>209072<br>05/22/97 | 209300           | 209746<br>04/07/98 | 209119 06/12/97    | 209215<br>08/21/97 | 209215<br>08/21/97 | PTA-843<br>10/13/99 | PTA-843<br>10/13/99 | PTA-843<br>10/13/99 | 209877<br>05/18/98 | 209641<br>02/25/98 | 209683 03/20/98  |
| cDNA<br>Clone ID                            | нндсм76                                 | HHGCM76                                 | HHGCQ54          | HHPEN62            | HIABB94            | HJACG02            | HJACG02            | HJACG30             | HJACG30             | HJACG30             | HJBCY35            | HJPAD75            | HKABZ65          |
|                                             |                                         |                                         |                  |                    |                    |                    |                    | 106                 | 901                 | 901                 |                    |                    | 109              |

| Last<br>AA of<br>ORF                        | 243              | 301                | 154                | 438                | 57               | 107                 | 107                 | 37                  | 234             | 46                 | 470                | 442                | 309                | 243                |
|---------------------------------------------|------------------|--------------------|--------------------|--------------------|------------------|---------------------|---------------------|---------------------|-----------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| First AA<br>of<br>Secreted<br>Portion       | 18               | 56                 | 56                 | 31                 | 30               | 42                  | 42                  |                     | 31              | 27                 | 16                 | 61                 | 2                  | 2                  |
| Last<br>of<br>Sig<br>Pep                    | 17               | 25                 | 25                 | 30                 | 29               | 14                  | 14                  |                     | 30              | 56                 | 15                 | 81                 | -                  | 1                  |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                | -                  | -                  | 1                  | ī                | -                   |                     | -                   | ī               | -                  | -                  | -                  | -                  | 1                  |
| AA<br>SEQ<br>ID<br>NO:                      | 802              | 514                | 402                | 515                | 710              | 516                 | 711                 | 712                 | 517             | 713                | 518                | 714                | 715                | 716                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 69               | 38                 | 35                 | 501                | 197              | 208                 | 208                 | 234                 | 178             | 30                 | 49                 | 14                 | 3                  | 3                  |
| 5' NT<br>of Start<br>Codon                  | 69               | 38                 | 35                 | 501                | 197              | 208                 | 208                 | 234                 | 178             | 30                 | 64                 | 14                 |                    |                    |
| 3' NT<br>of<br>Clone<br>Seq.                | 1611             | 3153               | 1626               | 2496               | 2351             | 1001                | 1001                | 699                 | 1142            | 417                | 2238               | 9061               | 1487               | 1525               |
| of<br>Clone<br>Seq.                         | 1                | -                  | -                  | 1                  | 1                | 270                 | 270                 | 1                   | 1038            | 1                  | -                  | -                  | -                  | 1                  |
| Total<br>NT<br>Seq.                         | 1611             | 3153               | 1626               | 2496               | 2351             | 1001                | 1001                | 699                 | 1142            | 417                | 2238               | 1949               | 1487               | 1525               |
| NT<br>SEQ<br>ID<br>NO:                      | 314              | 120                | 315                | 121                | 316              | 122                 | 317                 | 318                 | 123             | 319                | 124                | 320                | 321                | 322                |
| Vector                                      | pCMVSport<br>2.0 | pCMVSport<br>2.0   | pCMVSport<br>2.0   | pCMVSport<br>2.0   | pCMVSport<br>2.0 | pCMVSport<br>2.0    | pCMVSport<br>2.0    | pCMVSport<br>2.0    | pCMVSport 1     | pCMVSport 1        | ZAP Express        | ZAP Express        | ZAP Express        | ZAP Express        |
| ATCCTM Deposit No:Z and Date                | 209683           | 209346<br>10/09/97 | 209346<br>10/09/97 | 209627<br>02/12/98 | 209627           | PTA-849<br>10/13/99 | PTA-849<br>10/13/99 | PTA-849<br>10/13/99 | 209651 03/04/98 | 209651<br>03/04/98 | 209782<br>04/20/98 | 209782<br>04/20/98 | 209782<br>04/20/98 | 209782<br>04/20/98 |
| cDNA<br>Clone ID                            | HKABZ65          | HKACD58            | HKACD58            | HKAEV06            | HKAEV06          | HKAFT66             | HKAFT66             | HKAFT66             | HKB1E57         | HKB1E57            | HKFBC53            | HKFBC53            | HKFBC53            | HKFBC53            |
| Gene<br>No.                                 | 109              | 110                | 110                | 111                | 111              | 112                 | 112                 | 112                 | 113             | 113                | 114                | 114                | 114                | 114                |

| -                                    |          |         |         |                 |                    |                  | _                  |                    |                    | _                | _                  | _           | _           | _                |                    |
|--------------------------------------|----------|---------|---------|-----------------|--------------------|------------------|--------------------|--------------------|--------------------|------------------|--------------------|-------------|-------------|------------------|--------------------|
| Last<br>AA of<br>ORF                 |          | 260     | 148     | 95              | 41                 | 163              | 92                 | 113                | 161                | 348              | 4                  | 20          | 506         | 190              | 190                |
| First AA<br>of<br>Secreted           | Portion  | 34      | 34      | 20              | 22                 | 35               | 32                 | 21                 | 61                 | 24               | 22                 | 36          | 30          | 22               | 22                 |
| Last<br>AA<br>of<br>Sig              | Pep      | 33      | 33      | 19              | 21                 | 34               | 31                 | 20                 | 18                 | 23               | 21                 | 35          | 59          | 21               | 21                 |
| First<br>AA<br>of<br>Sig             | Pep      | 1       | -       | 1               | 1                  | 1                | 1                  | 1                  | 1                  | 1                | 1                  | 1           | 1           | 1                | -                  |
| AA<br>SEQ<br>ID<br>NO:               | Υ        | 519     | 717     | 520             | 521                | 522              | 718                | 523                | 524                | 525              | 526                | 527         | 528         | 529              | 719                |
| 5' NT<br>of First<br>AA of<br>Signal | Pep      | 53      | 55      | 130             | 202                | 238              | 45                 | 368                | 520                | 66               | 30                 | 186         | 249         | 01               | 3                  |
| 5' NT<br>of Start                    | Codon    | 53      | 55      | 130             | 202                | 238              | 45                 | 368                | 520                | 66               | 30                 | 186         | 249         | 10               | 3                  |
| 3° NT<br>of<br>Clone                 | Seq.     | 1052    | 1050    | 1439            | 1794               | 1346             | 717                | 1256               | 2572               | 1488             | 704                | 1022        | 1766        | 686              | 066                |
| 5' NT<br>of<br>Clone                 | Seq.     | 1       | 1       | -               | 1                  | 1                | -                  | 208                | 427                | -                | -                  | -           | -           | -                | -                  |
| Total<br>NT                          | Seq.     | 1052    | 1050    | 1492            | 1794               | 1346             | 720                | 1262               | 2572               | 1488             | 704                | 1022        | 1766        | 686              | 066                |
| NT<br>SEQ<br>ID<br>NO:               | Х        | 125     | 323     | 126             | 127                | 128              | 324                | 129                | 130                | 131              | 132                | 133         | 134         | 135              | 325                |
|                                      | Vector   | pSport1 | pSport1 | pBluescript     | pBluescript        | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0 | Uni-ZAP XR         | pCMVSport 1 | pCMVSport 1 | Lambda ZAP<br>II | Lambda ZAP<br>II   |
| ATCCTM Deposit No:Z and Date         |          | 209877  | 209877  | 209603 01/29/98 | 209463<br>11/14/97 | 209277           | 209277<br>09/18/97 | 209628<br>02/12/98 | 203027<br>06/26/98 | 203071           | 209746<br>04/07/98 | 203071      | 203517      | 209603 01/29/98  | 209603<br>01/29/98 |
| cDNA                                 | Clone ID | HKGDL36 | HKGDL36 | HKISB57         | HKMMW74            | HLDNA86          | HLDNA86            | HLDON23            | HLDQR62            | HLDQU79          | HLHAL68            | HLIBD68     | HLICQ90     | HLQDR48          | HLQDR48            |
| Gene                                 | No.      | 115     | 115     | 116             | 117                | 118              | 118                | 119                | 120                | 121              | 122                | 123         | 124         | 125              | 125                |

| Last<br>AA of<br>ORF                        | 7.5             | 26                   | 99                   | 299                  | 187                | 298                | 232              | 85                 | 46      | 11                 | 54      | 83                 | 73                 | 152                |
|---------------------------------------------|-----------------|----------------------|----------------------|----------------------|--------------------|--------------------|------------------|--------------------|---------|--------------------|---------|--------------------|--------------------|--------------------|
| First AA<br>of<br>Secreted<br>Portion       | 35              | 27                   | 27                   | 2                    | 16                 | 35                 | 28               | 37                 | 17      | 41                 | 40      | 30                 | 23                 | 25                 |
| Last<br>AA<br>of<br>Sig<br>Pep              | 34              | 26                   | 26                   | 1                    | 15                 | 34                 | 27               | 36                 | 16      | 40                 | 39      | 59                 | 22                 | 24                 |
| First<br>AA<br>of<br>Sig<br>Pep             | 1               | 1                    | -                    | 1                    | 1                  | 1                  | 1                | 1                  | 1       | 1                  | 1       | -                  | 1                  | 1                  |
| AA<br>SEQ<br>ID<br>NO:                      | 530             | 531                  | 720                  | 721                  | 532                | 533                | 534              | 535                | 536     | 537                | 722     | 538                | 539                | 540                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 5               | 226                  | 226                  | 3                    | 436                | 280                | 432              | 155                | 92      | 383                | 254     | 280                | 69                 | 161                |
| 5' NT<br>of Start<br>Codon                  | 2               | 226                  | 226                  |                      | 436                | 280                | 432              | 155                | 92      | 383                | 254     | 280                | 69                 | 161                |
| 3° NT<br>of<br>Clone<br>Seq.                | 2286            | 1170                 | 647                  | 1209                 | 266                | 2383               | 2081             | 646                | 312     | 770                | 729     | 1276               | 1223               | 864                |
| 5' NT<br>of<br>Clone<br>Seq.                | 1               | 1                    | -                    | 870                  | 246                | 157                | -                | 1                  | 1       | 1                  | 1       | -                  | -                  | 1                  |
| Total<br>NT<br>Seq.                         | 2286            | 1240                 | 647                  | 1321                 | 266                | 2383               | 2081             | 646                | 312     | 770                | 729     | 1276               | 1223               | 864                |
| SEQ NA                                      | 136             | 137                  | 326                  | 327                  | 138                | 139                | 140              | 141                | 142     | 143                | 328     | 144                | 145                | 146                |
| Vector                                      | Uni-ZAP XR      | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR           | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pSport1 | pSport1            | pSport1 | pSport1            | pSport1            | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z<br>and Date          | 209782 04/20/98 | PTA-2076<br>06/09/00 | PTA-2076<br>06/09/00 | PTA-2076<br>06/09/00 | 209626<br>02/12/98 | 203331<br>10/08/98 | 203517           | 209126<br>06/19/97 | 203071  | 209346<br>10/09/97 | 209346  | 209346<br>10/09/97 | 209853<br>05/07/98 | 209368<br>10/16/97 |
| cDNA<br>Clone ID                            | HLTHR66         | HLTIP94              | HLTIP94              | HLTIP94              | HLWAA17            | HLWBK05            | HLWBY76          | HLWCF05            | HLYAC95 | HLYAN59            | HLYAN59 | HLYAP91            | HLYES38            | HMADK33            |
| Gene<br>No.                                 | 126             | 127                  | 127                  | 127                  | 128                | 129                | 130              | 131                | 132     | 133                | 133     | 134                | 135                | 136                |

| Last<br>AA of              | ORF                 | 88                 | 340                  | 306                  | 49                 | 4          | 221              | 36                 | 62                 | 49                  | 64                  | 56                  | 20                  | 62         | 46                 |
|----------------------------|---------------------|--------------------|----------------------|----------------------|--------------------|------------|------------------|--------------------|--------------------|---------------------|---------------------|---------------------|---------------------|------------|--------------------|
| First AA                   | Secreted<br>Portion | 22                 | 27                   | 27                   | 28                 | 33         | 35               | 20                 | 28                 | 27                  | 27                  | 7                   | 7                   | 35         | 32                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 21                 | 26                   | 26                   | 27                 | 32         | 34               | 19                 | 27                 | 26                  | 26                  | 9                   | -                   | 34         | 31                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1                  | -                    | _                    | -                  | -          | -                | -                  | -                  | -                   | -                   | -                   | -                   | -          | -                  |
| SEQ<br>D                   | NO.                 | 541                | 542                  | 723                  | 543                | 544        | 545              | 546                | 547                | 548                 | 724                 | 725                 | 726                 | 549        | 550                |
| 5' NT<br>of First<br>AA of |                     | 267                | 4                    | 6                    | 175                | 273        | 34               | 332                | 92                 | 531                 | 528                 | 292                 | 7                   | 120        | 272                |
| ZY.S                       | of Start<br>Codon   | 267                | 4                    | 6                    | 175                | 273        | 34               | 332                | 92                 | 531                 | 528                 | 292                 |                     | 120        | 272                |
| 3' NT<br>of                | ο.                  | 1267               | 1258                 | 1084                 | 883                | 1465       | 1369             | 965                | 611                | 2497                | 1776                | 784                 | 427                 | 1217       | 1123               |
| 5° NT<br>of                | Clone<br>Seq.       | 1                  | 1                    | -                    | 1                  | 1          | 28               | -                  | 1                  | 1                   | 1                   | 1                   | 275                 | -          | 4                  |
| Total                      | Seq.                | 1267               | 1258                 | 1084                 | 883                | 1465       | 1369             | 969                | 629                | 2497                | 1776                | 784                 | 669                 | 1217       | 1123               |
| SEQ<br>ID                  | ÿ×                  | 147                | 148                  | 329                  | 149                | 150        | 151              | 152                | 153                | 154                 | 330                 | 331                 | 332                 | 155        | 156                |
|                            | Vector              | Uni-ZAP XR         | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR         | Uni-ZAP XR | Lambda ZAP<br>II | Lambda ZAP<br>II   | Lambda ZAP<br>II   | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z     | and Date            | 209563<br>12/18/97 | PTA-2075<br>06/09/00 | PTA-2075<br>06/09/00 | 209628<br>02/12/98 | 209368     | 209368           | 209243<br>09/12/97 | 209243<br>09/12/97 | PTA-842<br>10/13/99 | PTA-842<br>10/13/99 | PTA-842<br>10/13/99 | PTA-842<br>10/13/99 | 209368     | 209076<br>05/22/97 |
|                            | cDNA<br>Clone ID    | HMADS41            | HMAMIIS              | HMAMI15              | HMCFY13            | HMDAB56    | HMEED18          | HMEFT54            | HMEGF92            | HMSDL37             | HMSDL37             | HMSDL37             | HMSDL37             | HMSF126    | HMSJU68            |
|                            | Gene<br>No.         | 137                | 138                  | 138                  | 139                | 140        | 141              | 142                | 143                | 144                 | 144                 | 144                 | 144                 | 145        | 146                |

| _                          |                     |                     | _                   | _                  |                 | _                  | _                  | _                  | _          | _                  | _                  | _                  | _          |                    |                    |
|----------------------------|---------------------|---------------------|---------------------|--------------------|-----------------|--------------------|--------------------|--------------------|------------|--------------------|--------------------|--------------------|------------|--------------------|--------------------|
| Last<br>AA of              | ORF                 | 156                 | 957                 | 139                | 42              | 121                | 71                 | 89                 | 143        | 233                | 99                 | 113                | 82         | 06                 | 36                 |
| First AA                   | Secreted<br>Portion | 19                  | 61                  | 44                 | 31              | 78                 | 22                 | 13                 | 46         | 35                 | 22                 | 50                 | 16         | 24                 | 17                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 18                  | 18                  | 43                 | 30              | 27                 | 21                 | 12                 | 45         | 34                 | 21                 | 19                 | 15         | 23                 | 16                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1                   | -                   | -                  | 1               | 1                  | 1                  | -                  | 1          | 1                  | 1                  | 1                  | -          | 1                  | -                  |
| SEQ<br>B                   | NO.                 | 551                 | 727                 | 552                | 553             | 554                | 555                | 556                | 557        | 558                | 559                | 999                | 561        | 562                | 563                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 256                 | 255                 | 35                 | 124             | 72                 | 213                | 488                | 506        | 228                | 98                 | 185                | 72         | 108                | 135                |
| Z, Z                       | of Start<br>Codon   | 256                 | 255                 | 34                 | 124             | 72                 | 213                | 488                | 206        | 228                | 98                 | 185                | 72         | 108                | 135                |
| 3' NT<br>of                | Clone<br>Seq.       | 3388                | 3363                | 529                | 754             | 1346               | 1079               | 2058               | 1370       | 1212               | 919                | 524                | 1042       | 536                | 962                |
| S' NT<br>of                | Clone<br>Seq.       | -                   | -                   | -                  | 105             | -                  | -                  | 509                | 38         | 28                 | -                  | -                  | -          | -                  | -                  |
| Total                      | Seq.                | 3388                | 3546                | 529                | 1146            | 1346               | 1079               | 2103               | 1370       | 1212               | 919                | 524                | 1042       | 536                | 796                |
| SEQUE                      | ÿ×                  | 157                 | 333                 | 158                | 159             | 160                | 161                | 162                | 163        | 161                | 165                | 166                | 167        | 168                | 169                |
|                            | Vector              | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pSport1            | Uni-ZAP XR      | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR | pBluescript        | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR         | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z     | and Date            | PTA-322<br>07/09/99 | PTA-322<br>07/09/99 | 209628<br>02/12/98 | 209126 06/19/97 | 209368<br>10/16/97 | 209346<br>10/09/97 | 203027<br>06/26/98 | 203071     | 209628<br>02/12/98 | 209463<br>11/14/97 | 209299<br>09/25/97 | 209197     | 209407<br>10/23/97 | 209236<br>09/04/97 |
|                            | cDNA<br>Clone ID    | HMTBI36             | HMTBI36             | HMVBS81            | HMWDC28         | HMWFT65            | HNEEE24            | HNFFC43            | HNFGF20    | HNFIY77            | HNFJF07            | HNGDJ72            | HNGEP09    | HNGFR31            | HNGIJ31            |
|                            | Gene<br>No.         | 147                 | 147                 | 148                | 149             | 150                | 151                | 152                | 153        | 154                | 155                | 156                | 157        | 158                | 159                |

| Last<br>AA of              | ORF                 | 46         | 82         | 57                  | 57                  | 66                  | 81                 | 80                 | 8/              | 23                  | 80                   | 320              | 172                | 131                | 115                |
|----------------------------|---------------------|------------|------------|---------------------|---------------------|---------------------|--------------------|--------------------|-----------------|---------------------|----------------------|------------------|--------------------|--------------------|--------------------|
| First AA<br>of             | Secreted<br>Portion | 37         | 28         | 35                  | 35                  | 56                  | 35                 | 59                 | 22              | 21                  | 21                   | 36               | 36                 | 36                 | 24                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 36         | 27         | 34                  | 34                  | 25                  | 34                 | 28                 | 21              | 20                  | 20                   | 35               | 35                 | 35                 | 23                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1          | -          | -                   | 1                   | 1                   | 1                  | -                  | 1               | 1                   | 1                    | 1                | 1                  | -                  | 1                  |
| SEQ<br>B                   | Ν̈́ς<br>Υ           | 564        | 565        | 999                 | 728                 | 729                 | 567                | 568                | 569             | 570                 | 571                  | 572              | 730                | 731                | 573                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 11         | 388        | 27                  | 27                  | 969                 | 57                 | 38                 | 71              | 40                  | 12                   | 28               | 32                 | 16                 | 100                |
| 5' NT                      | of Start<br>Codon   | 11         | 388        | 27                  | 27                  |                     | 57                 | 38                 | 71              | 40                  | 12                   | 28               | 32                 | 16                 | 100                |
| 3°NT<br>of                 | Clone<br>Seq.       | 1037       | 841        | 2128                | 774                 | 1396                | 748                | 297                | 1891            | 1894                | 1355                 | 1382             | 1397               | 1368               | 791                |
| 5° NT<br>of                | Clone<br>Seq.       | 1          | -          | -                   | 1                   | 1                   | 1                  | -                  | 1               | 1                   | 1                    | 1                | -                  | -                  | 71                 |
| Total                      | Seq.                | 1037       | 841        | 2128                | 774                 | 1396                | 748                | 297                | 1891            | 1894                | 1355                 | 1382             | 1397               | 1368               | 791                |
| SEQ EI                     | ÿ×                  | 170        | 171        | 172                 | 334                 | 335                 | 173                | 174                | 175             | 176                 | 177                  | 178              | 336                | 337                | 179                |
|                            | Vector              | Uni-ZAP XR | Uni-ZAP XR | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR      | Uni-ZAP XR          | Uni-ZAP XR           | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0   |
| ATCCTM<br>Deposit No:Z     | and Date            | 209368     | 203648     | PTA-847<br>10/13/99 | PTA-847<br>10/13/99 | PTA-847<br>10/13/99 | 209628<br>02/12/98 | 209683<br>03/20/98 | 209683 03/20/98 | PTA-623<br>09/02/99 | PTA-1543<br>03/21/00 | 209563           | 209563<br>12/18/97 | 209563<br>12/18/97 | 209324<br>10/02/97 |
|                            | cDNA<br>Clone ID    | HNGJE50    | HNGND37    | HNGOI12             | HNGOI12             | HNGOI12             | HNHEU93            | HNHFM14            | HNHFR04         | HNHNB29             | HNHOD46              | HNTB126          | HNTB126            | HNTB126            | HNTBL27            |
|                            | Gene<br>No.         | 160        | 191        | 162                 | 162                 | 162                 | 163                | 491                | 165             | 166                 | 167                  | 168              | 168                | 168                | 169                |

| _                 | _            |                     |                      | _         | _       | _       | _               | _                   | _                   |                 | _          |                                          | _          |                     | _                   |                     |
|-------------------|--------------|---------------------|----------------------|-----------|---------|---------|-----------------|---------------------|---------------------|-----------------|------------|------------------------------------------|------------|---------------------|---------------------|---------------------|
| Last              | AA of        | Š                   | 402                  | 121       | 218     | 9/      | 46              | 68                  | 62                  | 87              | 41         | 35                                       | 43         | 484                 | 484                 | 266                 |
| First AA          | Jo .         | Secreted<br>Portion | 31                   | 59        | 20      | 34      | 34              | 32                  | 2                   | 21              | 24         | 27                                       | 22         | 25                  | 25                  | 25                  |
| Last              | of,          | Sig<br>Pep          | 30                   | 28        | 19      | 33      | 33              | 31                  | -                   | 20              | 23         | 26                                       | 21         | 24                  | 24                  | 24                  |
| First<br>AA       | jo           | Sig<br>Pep          | 1                    | -         |         | 1       | -               | 1                   | 1                   | 1               | 1          | 1                                        | 1          | 1                   | 1                   | 1                   |
| AA<br>SEQ         | Θ;           | ÿ⊁                  | 574                  | 73.2      | 575     | 576     | 733             | 577                 | 734                 | 578             | 579        | 580                                      | 581        | 582                 | 735                 | 736                 |
| 5' NT<br>of First | AA of        | Signal<br>Pep       | III                  | 57        | 270     | 307     | 306             | 257                 | 420                 | 166             | 46         | 434                                      | 358        | 49                  | 48                  | 78                  |
|                   |              | of Start<br>Codon   | 111                  | 57        | 270     | 307     | 306             | 257                 |                     | 166             | 46         |                                          | 358        | 49                  | 48                  | 78                  |
| 3' NT             | Jo .         | Clone<br>Seq.       | 2163                 | 1763      | 1979    | 2087    | 1114            | 1783                | 819                 | 1118            | 830        | 1939                                     | 739        | 2410                | 2409                | 876                 |
| S' NT             | Jo .         | Clone<br>Seq.       | 830                  | -         | -       | -       | -               | 265                 | 742                 | -               | -          | 294                                      | -          | -                   | -                   | -                   |
|                   | Total        | Seq.                | 2163                 | 1763      | 1979    | 2087    | 1274            | 1811                | 847                 | 1118            | 830        | 1939                                     | 739        | 2410                | 2409                | 876                 |
| NT<br>SEQ         | Ω;           | Öχ                  | 180                  | 338       | 181     | 182     | 339             | 183                 | 340                 | 184             | 185        | 186                                      | 187        | 188                 | 341                 | 342                 |
|                   |              | Vector              | pCMVSport            | pCMVSport | pSport1 | pSport1 | pSport1         | pSport1             | pSport1             | pSport1         | Uni-ZAP XR | Uni-ZAP XR                               | Uni-ZAP XR | pCMVSport<br>2.0    | pCMVSport<br>2.0    | pCMVSport<br>2.0    |
| ATCCTM            | Deposit No:Z | and Date            | PTA-1544<br>03/21/00 | PTA-1544  | 209782  | 209782  | 209782 04/20/98 | PTA-855<br>10/18/99 | PTA-855<br>10/18/99 | 203570 01/11/99 | 203069     | 209012<br>04/28/97<br>209089<br>06/05/97 | 203570     | PTA-848<br>10/13/99 | PTA-848<br>10/13/99 | PTA-848<br>10/13/99 |
|                   | i            | cDNA<br>Clone ID    | HNTCE26              | HNTCE26   | HNTNC20 | HNTN101 | HNTN101         | HNTSY18             | HNTSY18             | HOCNF19         | HODDF13    | HODDN92                                  | HODEJ32    | ноғмозз             | НОҒМQ33             | НОЕМQ33             |
|                   | · ·          | Gene<br>No.         | 170                  | 170       | 171     | 172     | 172             | 173                 | 173                 | 174             | 175        | 176                                      | 177        | 178                 | 178                 | 178                 |

|                                             | _                   |                     |                     |                     |                     |                     |                     |                     |                    |                    |            |                 |                    |                    |
|---------------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|--------------------|--------------------|------------|-----------------|--------------------|--------------------|
| Last<br>AA of<br>ORF                        | S                   | <u>\$</u>           | 184                 | 77                  | 84                  | 164                 | 161                 | 325                 | 99                 | 40                 | 40         | 296             | 41                 | 211                |
| First AA<br>of<br>Secreted<br>Portion       |                     | 2                   | 25                  | 7                   | 7                   | 22                  | 25                  | 7                   | 31                 | 61                 | 61         | 52              | 16                 | 19                 |
| Last<br>AA<br>of<br>Sig<br>Pep              |                     | -                   | 24                  | -                   | -                   | 21                  | 24                  | -                   | 30                 | 18                 | 18         | 51              | 15                 | 18                 |
| First<br>AA<br>of<br>Sig<br>Pep             | -                   | 1                   | -                   | -                   | 1                   | 1                   | -                   | -                   | -                  | -                  | -          | -               | -                  | -                  |
| SEQ<br>NO:                                  | 737                 | 738                 | 583                 | 739                 | 740                 | 584                 | 741                 | 742                 | 585                | 586                | 743        | 587             | 588                | 589                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 724                 | 123                 | 170                 | 2                   | 54                  | 361                 | 102                 | 55                  | 68                 | 1076               | 146        | 808             | 51                 | 128                |
| 5' NT<br>of Start<br>Codon                  |                     |                     | 170                 |                     |                     | 361                 | 102                 |                     | 68                 | 1076               | 146        | 508             | 51                 | 128                |
| 3' NT<br>of<br>Clone<br>Seq.                | 1586                | 1011                | 3369                | 1063                | 1178                | 3530                | 585                 | 1942                | 1145               | 2214               | 1258       | 4693            | 813                | 1739               |
| 5' NT<br>of<br>Clone<br>Seq.                | -                   | 873                 | -                   | 533                 | -                   | -                   | 29                  | 1339                | -                  | 985                | -          | -               | -                  | -                  |
| Total<br>NT<br>Seq.                         | 1586                | 1011                | 3369                | 1063                | 1178                | 3530                | 585                 | 4344                | 1145               | 2214               | 1258       | 4712            | 813                | 1739               |
| SEQ SEX                                     | 343                 | 344                 | 189                 | 345                 | 346                 | 190                 | 347                 | 348                 | 161                | 192                | 349        | 193             | 194                | 195                |
| Vector                                      | pCMVSport           | pCMVSport<br>2.0    | pCMVSport<br>2.0    | pCMVSport<br>2.0    | pCMVSport<br>2.0    | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR      | Uni-ZAP XR         | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z<br>and Date          | PTA-848<br>10/13/99 | PTA-848<br>10/13/99 | PTA-867<br>10/26/99 | PTA-867<br>10/26/99 | PTA-867<br>10/26/99 | PTA-845<br>10/13/99 | PTA-845<br>10/13/99 | PTA-845<br>10/13/99 | 209551<br>12/12/97 | 209423<br>10/30/97 | 209423     | 209086 05/29/97 | 209244<br>09/12/97 | 209563<br>12/18/97 |
| cDNA<br>Clone ID                            | НОЕМQ33             | НОЕМQ33             | HOHBY44             | HOHBY44             | HOHBY44             | ноовля2             | ноовля2             | ноовля2             | HOSBY40            | HOSDJ25            | HOSDJ25    | HOUCQ17         | HPEAD79            | HPIBO15            |
| Gene<br>No.                                 | 178                 | 178                 | 179                 | 179                 | 179                 | 180                 | 180                 | 180                 | 181                | 182                | 182        | 183             | 184                | 185                |

| 5                          | i ne.               | 1          |                 | _                   |                     |                     |                     | _                    | ı —                  |                      |                    |            | _          | _                  |                    |
|----------------------------|---------------------|------------|-----------------|---------------------|---------------------|---------------------|---------------------|----------------------|----------------------|----------------------|--------------------|------------|------------|--------------------|--------------------|
| Last<br>AA of              | ORF                 | 173        | 53              | 84                  | 84                  | 10                  | 4                   | 8                    | 80                   | 145                  | 201                | 201        | 420        | 392                | 63                 |
| First AA<br>of             | Secreted<br>Portion | 61         | 32              | 19                  | 19                  |                     |                     | 36                   | 36                   | 7                    | 26                 | 26         | 30         | 30                 | 43                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 18         | 31              | 18                  | 18                  |                     |                     | 35                   | 35                   | -                    | 25                 | 25         | 59         | 29                 | 42                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1          | -               | -                   | 1                   | 1                   | 1                   | 1                    | 1                    | 1                    | 1                  | 1          | 1          | -                  | 1                  |
| AA<br>SEQ<br>ID            | S >                 | 744        | 590             | 591                 | 745                 | 746                 | 747                 | 592                  | 748                  | 749                  | 593                | 750        | 594        | 751                | 752                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 127        | 236             | 126                 | 119                 | 696                 | 509                 | 98                   | 136                  | 232                  | 49                 | 28         | 62         | 0/                 | 148                |
| S' NT                      | of Start<br>Codon   | 127        | 236             | 126                 | 119                 |                     | 509                 | 98                   | 136                  |                      | 64                 | 28         | 62         | 70                 | 148                |
| 3, NT<br>of                | Clone<br>Seq.       | 1739       | 1677            | 2648                | 538                 | 1346                | 912                 | 3107                 | 966                  | 751                  | 1084               | 1083       | 2072       | 1775               | 998                |
| 5° NT<br>of                | Clone<br>Seq.       | -          | -               | -                   | -                   | 1                   | -                   | -                    | 28                   | 183                  | -                  | 1          | -          | 1038               | 128                |
| Total                      | Seq.                | 1739       | 1677            | 2648                | 538                 | 1346                | 912                 | 3107                 | 995                  | 751                  | 1084               | 11.77      | 2072       | 1775               | 998                |
| SEQ<br>ID                  | ÿ×                  | 350        | 196             | 197                 | 351                 | 352                 | 353                 | 198                  | 354                  | 355                  | 199                | 356        | 200        | 357                | 358                |
|                            | Vector              | Uni-ZAP XR | Uni-ZAP XR      | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR | Uni-ZAP XR         | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z     | and Date            | 209563     | 209889 05/22/98 | PTA-855<br>10/18/99 | PTA-855<br>10/18/99 | PTA-855<br>10/18/99 | PTA-855<br>10/18/99 | PTA-2071<br>06/09/00 | PTA-2071<br>06/09/00 | PTA-2071<br>06/09/00 | 209628<br>02/12/98 | 209628     | 209195     | 209195<br>08/01/97 | 209195<br>08/01/97 |
|                            | cDNA<br>Clone ID    | HPIBO15    | HPJB133         | HPJBK12             | HPJBK12             | HPJBK12             | HPJBK12             | HPJCL22              | HPJCL22              | HPJCL22              | HPMDK28            | HPMDK28    | HPRAL78    | HPRAL78            | HPRAL78            |
|                            | Gene<br>No.         | 185        | 186             | 187                 | 187                 | 187                 | 187                 | 188                  | 188                  | 188                  | 189                | 189        | 190        | 190                | 190                |

| 5                                           | 1                |                  | _                  |                    |                  |                    |                    | _                   |                     |                     |                     | _                    | _                    |                      |
|---------------------------------------------|------------------|------------------|--------------------|--------------------|------------------|--------------------|--------------------|---------------------|---------------------|---------------------|---------------------|----------------------|----------------------|----------------------|
| Last<br>AA of<br>ORF                        | 102              | 102              | 53                 | 53                 | 472              | 472                | 178                | 359                 | 199                 | 7                   | 32                  | 379                  | 283                  | 286                  |
| First AA<br>of<br>Secreted<br>Portion       | 28               | 78               | 41                 | 41                 | 25               | 25                 | 7                  | 28                  | 39                  |                     | 11                  | 31                   | 16                   | 16                   |
| Last<br>of<br>Sig<br>Pep                    | 27               | 27               | 40                 | 40                 | 24               | 24                 | -                  | 27                  | 38                  |                     | 10                  | 30                   | 15                   | 15                   |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                | -                | _                  | -                  | -                | -                  | -                  | -                   | -                   | -                   | -                   | -                    | -                    | 1                    |
| A Sig B Sig ⊁                               | 595              | 753              | 596                | 754                | 597              | 755                | 756                | 598                 | 757                 | 758                 | 759                 | 599                  | 760                  | 761                  |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 4                | 130              | 252                | 252                | 132              | 66                 | -                  | 30                  | 30                  | 11                  | 1048                | 01                   | 31                   | 247                  |
| 5' NT<br>of Start<br>Codon                  | 144              | 130              | 252                | 252                | 132              | 66                 |                    | 30                  | 30                  |                     |                     | 10                   | 31                   | 247                  |
| 3' NT<br>of<br>Clone<br>Seq.                | 1251             | 1237             | 1539               | 1453               | 2077             | 1863               | 1134               | 2108                | 979                 | 152                 | 1760                | 1146                 | 880                  | 1106                 |
| 5' NT<br>of<br>Clone<br>Seq.                | -                | 1                | 24                 | 24                 | 1                | 8                  | -                  | 1                   | 8                   | 1                   | 127                 | 224                  | -                    | 224                  |
| Total<br>NT<br>Seq.                         | 1251             | 1237             | 1539               | 1681               | 2077             | 1863               | 1134               | 2108                | 626                 | 152                 | 1760                | 1146                 | 880                  | 1106                 |
| N N B S N                                   | 201              | 357              | 202                | 360                | 203              | 361                | 362                | 204                 | 363                 | 364                 | 365                 | 205                  | 366                  | 367                  |
| Vector                                      | pCMVSport<br>3.0 | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0 | pCMVSport<br>3.0   | pCMVSport<br>3.0   | Uni-ZAP XR           | Uni-ZAP XR           | Uni-ZAP XR           |
| ATCCTM<br>Deposit No:Z<br>and Date          | 209889           | 209889           | 209852<br>05/07/98 | 209852<br>05/07/98 | 209878 05/18/98  | 209878<br>05/18/98 | 209878<br>05/18/98 | PTA-841<br>10/13/99 | PTA-841<br>10/13/99 | PTA-841<br>10/13/99 | PTA-841<br>10/13/99 | PTA-2069<br>06/09/00 | PTA-2069<br>06/09/00 | PTA-2069<br>06/09/00 |
| cDNA<br>Clone ID                            | HRABA80          | HRABA80          | HRACD15            | HRACD15            | HRACJ35          | HRACJ35            | HRACJ35            | HRGBL78             | HRGBL78             | HRGBL78             | HRGBL78             | HROAJ39              | HROAJ39              | HROAJ39              |
| Gene<br>No.                                 | 161              | 161              | 192                | 192                | 193              | 193                | 193                | 194                 | 194                 | 194                 | 194                 | 195                  | 195                  | 195                  |

|                                             |            |                 | _                  | _                  |                 |            |            |                    |                 | _                  |             |                    |                    |                   |
|---------------------------------------------|------------|-----------------|--------------------|--------------------|-----------------|------------|------------|--------------------|-----------------|--------------------|-------------|--------------------|--------------------|-------------------|
| Last<br>AA of<br>ORF                        | 48         | 142             | 45                 | 399                | 305             | 223        | 72         | 152                | 40              | 135                | 121         | 72                 | 28                 | 182               |
| First AA<br>of<br>Secreted<br>Portion       | 23         | 27              | 30                 | 20                 | 22              | 21         | 20         | 21                 | 56              | 18                 | 18          | 14                 | 23                 | 24                |
| Last<br>AA<br>of<br>Sig<br>Pep              | 22         | 26              | 29                 | 19                 | 21              | 20         | 19         | 20                 | 25              | 17                 | 17          | 13                 | 22                 | 23                |
| First<br>AA<br>of<br>Sig<br>Pep             | 1          | 1               | _                  | -                  | -               | -          | -          | -                  | -               | -                  | -           | -                  | -                  | -                 |
| SEQ<br>NÖ:P                                 | 009        | 109             | 762                | 602                | 763             | 603        | 764        | 604                | 605             | 909                | 765         | 607                | 809                | 609               |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 122        | 142             | 122                | 09                 | 126             | 66         | 66         | 247                | 351             | 16                 | 22          | 177                | ∞                  | 14                |
| 5' NT<br>of Start<br>Codon                  | 122        | 142             | 122                | 09                 | 126             | 66         | 66         | 247                | 351             | 16                 | 22          | 177                | ∞                  | 14                |
| 3° NT<br>of<br>Clone<br>Seq.                | 1998       | 970             | 646                | 1782               | 1590            | 1179       | 1179       | 1443               | 261             | 808                | 618         | 1986               | 1303               | 587               |
| 5' NT<br>of<br>Clone<br>Seq.                | -          | 106             | 1                  | 1                  | 96              | 23         | 1          | 1                  | 1               | 1                  | 1           | -                  | -                  | 1                 |
| Total<br>NT<br>Seq.                         | 8661       | 026             | 646                | 1782               | 1590            | 1205       | 1179       | 1443               | 195             | 809                | 618         | 1986               | 1303               | 587               |
| SEQ<br>NO B                                 | 206        | 207             | 368                | 208                | 369             | 209        | 370        | 210                | 211             | 212                | 371         | 213                | 214                | 215               |
| Vector                                      | Uni-ZAP XR | Uni-ZAP XR      | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR      | Uni-ZAP XR | Uni-ZAP XR | Uni-ZAP XR         | Uni-ZAP XR      | pBluescript        | pBluescript | Uni-ZAP XR         | Uni-ZAP XR         | Uni-ZAP XR        |
| ATCCTM Deposit No:Z and Date                | 203499     | 209126 06/19/97 | 209126<br>06/19/97 | 209603<br>01/29/98 | 209603 01/29/98 | 203648     | 203648     | 203081<br>07/30/98 | 209148 07/17/97 | 209145<br>07/17/97 | 209145      | 209853<br>05/07/98 | 209551<br>12/12/97 | 97924<br>03/07/97 |
| cDNA<br>Clone ID                            | нковр68    | HSAWD74         | HSAWD74            | HSDEK49            | HSDEK49         | HSDFJ26    | HSDFJ26    | HSDJA15            | HSDJM31         | HSDSB09            | HSDSB09     | HSHAX21            | HSIDJ81            | HSJBQ79           |
| Gene<br>No.                                 | 196        | 197             | 197                | 198                | 198             | 199        | 199        | 200                | 201             | 202                | 202         | 203                | 204                | 205               |

|                                             | _          |                | _                   | _                   |                     |                                         |                                         | _                  |                    | _          | _          | _                  |                     |
|---------------------------------------------|------------|----------------|---------------------|---------------------|---------------------|-----------------------------------------|-----------------------------------------|--------------------|--------------------|------------|------------|--------------------|---------------------|
| Last<br>AA of<br>ORF                        | 327        | <del>2</del> 8 | 950                 | 509                 | 554                 | 260                                     | 23                                      | 82                 | 35                 | 22         | 25         | 78                 | 41                  |
| First AA<br>of<br>Secreted<br>Portion       | 20         | 24             | 25                  | 22                  | 22                  | 24                                      | 19                                      | 26                 | 50                 | 61         | 81         | 33                 | 61                  |
| Last<br>AA<br>of<br>Sig<br>Pep              | 61         | 23             | 24                  | 21                  | 21                  | 23                                      | 81                                      | 25                 | 61                 | 18         | 17         | 32                 | 18                  |
| First<br>AA<br>of<br>Sig<br>Pep             | -          | 1              | -                   | -                   | -                   | -                                       | -                                       |                    | -                  | -          | -          | -                  | -                   |
| AA<br>SEQ<br>BD<br>NO:                      | 992        | 767            | 019                 | 292                 | 692                 | 119                                     | 770                                     | 612                | 613                | 614        | 171        | 615                | 919                 |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 57         | 35             | 786                 | 127                 | 12                  | 353                                     | 537                                     | 484                | 220                | 225        | 232        | 96                 | 82                  |
| 5' NT<br>of Start<br>Codon                  | 57         | 35             | 786                 | 127                 | 12                  | 353                                     | 537                                     | 484                | 220                | 225        | 232        | 96                 | 82                  |
| 3° NT<br>of<br>Clone<br>Seq.                | 809        | 286            | 4412                | 1792                | 1673                | 1432                                    | 2084                                    | 1334               | 198                | 587        | 720        | 477                | 1925                |
| of<br>Clone<br>Seq.                         | 164        | 4              | -                   | 134                 | -                   | 151                                     | 335                                     | 449                | -                  | 1          | -          | -                  | -                   |
| Total<br>NT<br>Seq.                         | 1507       | 989            | 4412                | 1792                | 1673                | 1907                                    | 2084                                    | 1334               | 861                | 587        | 720        | 477                | 1930                |
| FSBBS×                                      | 372        | 373            | 216                 | 374                 | 375                 | 217                                     | 376                                     | 218                | 219                | 220        | 377        | 221                | 222                 |
| Vector                                      | Uni-ZAP XR | Uni-ZAP XR     | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | pBluescript                             | pBluescript                             | pBluescript        | Uni-ZAP XR         | Uni-ZAP XR | Uni-ZAP XR | Uni-ZAP XR         | Uni-ZAP XR          |
| ATCCTM<br>Deposit No:Z<br>and Date          | 97924      | 97924 03/07/97 | PTA-322<br>07/09/99 | PTA-322<br>07/09/99 | PTA-322<br>07/09/99 | 97977<br>04/04/97<br>209082<br>05/29/97 | 97977<br>04/04/97<br>209082<br>05/29/97 | 209346<br>10/09/97 | 209139<br>07/03/97 | 209300     | 209300     | 209126<br>06/19/97 | PTA-622<br>09/02/99 |
| cDNA<br>Clone ID                            | HSJBQ79    | HSJBQ79        | HSKDA27             | HSKDA27             | HSKDA27             | HSKGN81                                 | HSKGN81                                 | HSKNB56            | HSNAD72            | HSNMC45    | HSNMC45    | HSQFP66            | HSRFZ57             |
| Gene<br>No.                                 | 205        | 205            | 206                 | 206                 | 206                 | 207                                     | 207                                     | 208                | 209                | 210        | 210        | 211                | 212                 |

| Last<br>AA of<br>ORF                        | 95                                       | 06                 | 22                  | 434                 | 40                  | 305                | 305              | 364                  | 282                 | 122                 | 216                 | 87                                      | 178                |
|---------------------------------------------|------------------------------------------|--------------------|---------------------|---------------------|---------------------|--------------------|------------------|----------------------|---------------------|---------------------|---------------------|-----------------------------------------|--------------------|
| First AA<br>of<br>Secreted<br>Portion       | 32                                       | 61                 | 22                  | 31                  | 22                  | 25                 | 25               | 33                   | 34                  | 34                  | 2                   | 23                                      | 16                 |
| Last<br>AA<br>of<br>Sig<br>Pep              | 31                                       | 81                 | 21                  | 30                  | 21                  | 24                 | 24               | 32                   | 33                  | 33                  | -                   | 22                                      | 15                 |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                                        | 1                  | 1                   | 1                   | 1                   | 1                  | 1                | 1                    | 1                   | 1                   | 1                   | -                                       | 1                  |
| SEQ A                                       | 617                                      | 819                | 619                 | 620                 | 772                 | 621                | 773              | 622                  | 623                 | 774                 | 775                 | 624                                     | 625                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 153                                      | 256                | 87                  | 448                 | 215                 | 47                 | 48               | 65                   | 319                 | 372                 | 124                 | 38                                      | 13                 |
| 5' NT<br>of Start<br>Codon                  | 153                                      | 256                | 87                  | 448                 | 215                 | 47                 | 48               | 65                   | 319                 | 372                 |                     | 38                                      | 13                 |
| 3' NT<br>of<br>Clone<br>Seq.                | 1021                                     | 727                | 1256                | 3347                | 1707                | 1238               | 1239             | 1481                 | 1341                | 738                 | 807                 | 912                                     | 839                |
| of<br>Clone<br>Seq.                         | -                                        | -                  | 1                   | 1655                | -                   | -                  | -                | 54                   | -                   | 159                 | -                   | _                                       | -                  |
| Total<br>NT<br>Seq.                         | 1021                                     | 727                | 1256                | 3466                | 1707                | 1238               | 1239             | 1481                 | 1341                | 738                 | 935                 | 912                                     | 839                |
| SEQ H ⊗ ×                                   | 223                                      | 224                | 225                 | 226                 | 378                 | 227                | 379              | 228                  | 229                 | 380                 | 381                 | 230                                     | 231                |
| Vector                                      | Uni-ZAP XR                               | Uni-ZAP XR         | Uni-ZAP XR          | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pCMVSport<br>3.0   | pCMVSport<br>3.0 | Uni-ZAP XR           | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | pSportl                                 | Uni-ZAP XR         |
| ATCCTM Deposit No:Z and Date                | 209007<br>04/28/97<br>209083<br>05/29/97 | 209603<br>01/29/98 | PTA-499<br>08/11/99 | PTA-163<br>06/01/99 | PTA-163<br>06/01/99 | 209463<br>11/14/97 | 209463           | PTA-1543<br>03/21/00 | PTA-843<br>10/13/99 | PTA-843<br>10/13/99 | PTA-843<br>10/13/99 | 97974<br>04/04/97<br>209080<br>05/29/97 | 209877<br>05/18/98 |
| cDNA<br>Clone ID                            | HSUBW09                                  | HSVBU91            | HSXGI47             | HSYAZ63             | HSYAZ63             | HSYBG37            | HSYBG37          | HTADW91              | HTAEE28             | HTAEE28             | HTAEE28             | HTDAF28                                 | HTECC05            |
| Gene<br>No.                                 | 213                                      | 214                | 215                 | 216                 | 216                 | 217                | 217              | 218                  | 219                 | 219                 | 219                 | 220                                     | 221                |

|                                             | _          | _          |                                         |                    |                                         |                                         |                                         |                                         | _          |                      |
|---------------------------------------------|------------|------------|-----------------------------------------|--------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|------------|----------------------|
| Last<br>AA of<br>ORF                        | 127        | 164        | 298                                     | 46                 | 99                                      | 208                                     | 159                                     | 11                                      | 44         | 158                  |
| First AA<br>of<br>Secreted<br>Portion       | 91         | 91         | 23                                      | 25                 | 44                                      | 16                                      | 16                                      | 20                                      | 21         | 18                   |
| Last<br>of<br>Sig<br>Pep                    | 15         | 15         | 22                                      | 24                 | 43                                      | 15                                      | 15                                      | 61                                      | 20         | 17                   |
| First<br>AA<br>of<br>Sig<br>Pep             | 1          | -          | -                                       | 1                  | 1                                       | 1                                       | -                                       | 1                                       | 1          | 1                    |
| AA SEQ AY NÖ: AY                            | 776        | 777        | 626                                     | 627                | 628                                     | 620                                     | 778                                     | 677                                     | 630        | 631                  |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 21         | 27         | 65                                      | 231                | 96                                      | 156                                     | 163                                     | 155                                     | 164        | 15                   |
| 5' NT<br>of Start<br>Codon                  | 21         | 27         | 65                                      | 231                | 06                                      | 951                                     | 163                                     | 155                                     | 164        | 15                   |
| 3' NT<br>of<br>Clone<br>Seq.                | 871        | 881        | 1022                                    | 1028               | 450                                     | 1094                                    | 1147                                    | 1134                                    | 808        | 1898                 |
| of<br>Olone<br>Seq.                         | 1          | -          | 20                                      | -                  | -                                       | -                                       | -                                       | _                                       | -          | 1                    |
| Total<br>NT<br>Seq.                         | 871        | 881        | 1022                                    | 1028               | 450                                     | 1094                                    | 1147                                    | 1134                                    | 808        | 1898                 |
| SE G S ×                                    | 382        | 383        | 232                                     | 233                | 234                                     | 235                                     | 384                                     | 385                                     | 236        | 237                  |
| Vector                                      | Uni-ZAP XR | Uni-ZAP XR | Uni-ZAP XR                              | Uni-ZAP XR         | Uni-ZAP XR                              | Uni-ZAP XR                              | Uni-ZAP XR                              | Uni-ZAP XR                              | Uni-ZAP XR | Uni-ZAP XR           |
| ATCCTM Deposit No:Z and Date                | 209877     | 209877     | 97922<br>03/07/97<br>209070<br>05/22/97 | 209324<br>10/02/97 | 97958<br>03/13/97<br>209072<br>05/22/97 | 97958<br>03/13/97<br>209072<br>05/22/97 | 97958<br>03/13/97<br>209072<br>05/22/97 | 97958<br>03/13/97<br>209072<br>05/22/97 | 203648     | PTA-1544<br>03/21/00 |
| cDNA<br>Clone ID                            | HTECC05    | HTECC05    | HTEBB42                                 | HTEFU65            | HTEGA76                                 | HTEIN13                                 | HTEJN13                                 | HTEIN13                                 | HTELP17    | HTELS08              |
| Gene<br>No.                                 | 221        | 221        | 222                                     | 223                | 224                                     | 225                                     | 225                                     | 225                                     | 226        | 227                  |

|                            |                     | _                  | _                  | _                  | _                  |                     | _                   | _                   |                 |                    | _                   |                     |                     | _                  |                    |
|----------------------------|---------------------|--------------------|--------------------|--------------------|--------------------|---------------------|---------------------|---------------------|-----------------|--------------------|---------------------|---------------------|---------------------|--------------------|--------------------|
| Last<br>AA of              | ORF                 | 101                | 231                | 11                 | 1/2                | 230                 | 140                 | 98                  | 37              | 133                | 42                  | 42                  | 92                  | 44                 | 111                |
| First AA<br>of             | Secreted<br>Portion | 44                 | 12                 | 30                 | 30                 | 25                  | 25                  | 2                   | 35              | 23                 | 81                  | 81                  | 2                   | 26                 | 61                 |
| Last<br>AA<br>of           | Sig<br>Pep          | 43                 | 14                 | 29                 | 29                 | 24                  | 24                  | -                   | 34              | 22                 | 17                  | 17                  | -                   | 25                 | 18                 |
| First<br>AA<br>of          | Sig<br>Pep          | 1                  | -                  | -                  | 1                  | 1                   | 1                   | -                   | 1               | 1                  | 1                   | 1                   | -                   | -                  | 1                  |
| AA<br>SEQ<br>ID            | ος<br>γ             | 632                | 633                | 634                | 780                | 635                 | 781                 | 782                 | 636             | 637                | 637                 | 783                 | 784                 | 639                | 640                |
| 5' NT<br>of First<br>AA of | Signal<br>Pep       | 73                 | 91                 | 2365               | 530                | 811                 | III                 | 96                  | 170             | 133                | 95                  | 100                 | 175                 | 185                | 16                 |
| 5' NT                      | of Start<br>Codon   | 73                 | 91                 | 2365               | 530                | 118                 | 111                 |                     | 170             | 133                | 95                  | 100                 |                     | 185                | 91                 |
| 3° NT<br>of                | Clone<br>Seq.       | 818                | 1558               | 3431               | 1598               | 1481                | 530                 | 1046                | 652             | 1711               | 2058                | 618                 | 501                 | 407                | 675                |
| s, NT<br>of                | Clone<br>Seq.       | 1                  | -                  | 2141               | 306                | -                   | 1                   | 359                 | 1               | 1                  | 1                   | 1                   | -                   | -                  | 1                  |
| Total                      | NT<br>Seq.          | 818                | 1558               | 3435               | 1598               | 1481                | 530                 | 1046                | 652             | 1711               | 2058                | 618                 | 501                 | 407                | 675                |
| NT<br>SEQ<br>ID            | ÿ×                  | 238                | 239                | 240                | 386                | 241                 | 387                 | 388                 | 242             | 243                | 244                 | 389                 | 390                 | 245                | 246                |
|                            | Vector              | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | pBluescript     | Uni-ZAP XR         | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR          | Lambda ZAP<br>II   | Uni-ZAP XR         |
| ATCCTM<br>Deposit No:Z     | and Date            | 209641<br>02/25/98 | 209852<br>05/07/98 | 209423<br>10/30/97 | 209423<br>10/30/97 | PTA-871<br>10/26/99 | PTA-871<br>10/26/99 | PTA-871<br>10/26/99 | 209138 07/03/97 | 209641<br>02/25/98 | PTA-841<br>10/13/99 | PTA-841<br>10/13/99 | PTA-841<br>10/13/99 | 209651<br>03/04/98 | 209423<br>10/30/97 |
|                            | cDNA<br>Clone ID    | HTLEP53            | HTOIV21            | HTPCS72            | HTPCS72            | нтрін83             | нтрін83             | нтрін83             | HTSEW17         | HTTBI76            | HTTBS64             | HTTBS64             | HTTBS64             | HTWKE60            | HTXAJ12            |
|                            | Gene<br>No.         | 877                | 229                | 230                | 230                | 231                 | 231                 | 231                 | 232             | 233                | 234                 | 234                 | 234                 | 235                | 236                |

|                                             |            |                    | _                   |                     |            | _                  | _                  |                  |                  |                  |                      |                    |                    |                     |
|---------------------------------------------|------------|--------------------|---------------------|---------------------|------------|--------------------|--------------------|------------------|------------------|------------------|----------------------|--------------------|--------------------|---------------------|
| Last<br>AA of<br>ORF                        | Ξ          | 99                 | 78                  | 78                  | 25         | 20                 | 45                 | 168              | 23               | 691              | 43                   | 105                | 105                | 1887                |
| First AA<br>of<br>Secreted<br>Portion       | 61         | 61                 | 29                  | 29                  | 23         | 30                 | 21                 | 31               | 31               | 31               | 7                    | 22                 | 22                 | 26                  |
| Last<br>AA<br>of<br>Sig<br>Pep              | 81         | 81                 | 28                  | 28                  | 22         | 29                 | 20                 | 30               | 30               | 30               | -                    | 21                 | 21                 | 25                  |
| First<br>AA<br>of<br>Sig<br>Pep             | -          | -                  | -                   | -                   | -          | -                  | -                  | -                | -                | -                | -                    | -                  | -                  | 1                   |
| AA<br>SEQ<br>NÖ:                            | 785        | 4                  | 542                 | 786                 | 543        | 4                  | 645                | 646              | 787              | 788              | 647                  | 648                | 789                | 649                 |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 16         | 328                | 421                 | 330                 | 72         | 123                | 14                 | 322              | 322              | 312              | 185                  | 243                | 233                | 75                  |
| 5' NT<br>of Start<br>Codon                  | 16         | 328                | 421                 | 330                 | 72         | 123                | 41                 | 322              | 322              | 312              | 581                  | 243                | 233                | 75                  |
| 3° NT<br>of<br>Clone<br>Seq.                | 519        | 2398               | 996                 | 875                 | 1505       | 898                | 1502               | 3308             | 3306             | 2194             | 6921                 | 1138               | 1138               | 6259                |
| of<br>Olone<br>Seq.                         | -          | 211                | 170                 | 79                  | -          | -                  | -                  | -                | -                | -                | 529                  | -                  | -                  | 1                   |
| Total<br>NT<br>Seq.                         | 675        | 2398               | 975                 | 884                 | 1505       | 898                | 1502               | 3308             | 3306             | 2194             | 1769                 | 1138               | 1138               | 6259                |
| SEQ N                                       | 391        | 247                | 248                 | 392                 | 249        | 250                | 251                | 252              | 393              | 394              | 253                  | 254                | 395                | 255                 |
| Vector                                      | Uni-ZAP XR | Uni-ZAP XR         | Uni-ZAP XR          | Uni-ZAP XR          | Uni-ZAP XR | pSport1            | Uni-ZAP XR         | pCMVSport<br>3.0 | pCMVSport<br>3.0 | pCMVSport<br>3.0 | pCMVSport<br>3.0     | pCMVSport<br>3.0   | pCMVSport<br>3.0   | pCMVSport<br>3.0    |
| ATCCTM<br>Deposit No:Z<br>and Date          | 209423     | 209580<br>01/14/98 | PTA-622<br>09/02/99 | PTA-622<br>09/02/99 | 203648     | 209641<br>02/25/98 | 209603<br>01/29/98 | 203570           | 203570           | 203570           | PTA-1543<br>03/21/00 | 209641<br>02/25/98 | 209641<br>02/25/98 | PTA-868<br>10/26/99 |
| cDNA<br>Clone ID                            | HTXAJ12    | HTXJM03            | HTXKF95             | HTXKF95             | HTXON32    | HUFCJ30            | HUVEB53            | HWAAD63          | HWAAD63          | HWAAD63          | HWADJ89              | HWBCP79            | HWBCP79            | HWBEM18             |
| Gene<br>No.                                 | 236        | 237                | 238                 | 238                 | 239        | 240                | 241                | 242              | 242              | 242              | 243                  | 244                | 244                | 245                 |

|                                             |                     | _                   |                      | _                   |            |                                         | _                   | _                  |
|---------------------------------------------|---------------------|---------------------|----------------------|---------------------|------------|-----------------------------------------|---------------------|--------------------|
| Last<br>AA of<br>ORF                        | 988                 | 498                 | 52                   | 346                 | 155        | 30                                      | 363                 | 122                |
| First AA<br>of<br>Secreted<br>Portion       | 26                  | 7                   | 2                    | 31                  | 24         | 24                                      | 22                  | 42                 |
| Last<br>AA<br>of<br>Sig<br>Pep              | 25                  | -                   | _                    | 30                  | 23         | 23                                      | 21                  | 41                 |
| First<br>AA<br>of<br>Sig<br>Pep             | 1                   | -                   | -                    | 1                   | 1          | 1                                       | 1                   | -                  |
| AA<br>SEQ<br>ID<br>NO:<br>Y                 | 790                 | 791                 | 650                  | 159                 | 652        | 653                                     | 654                 | 655                |
| 5' NT<br>of First<br>AA of<br>Signal<br>Pep | 99                  | _                   | 271                  | 33                  | 139        | 166                                     | 9/                  | 28                 |
| 5' NT<br>of Start<br>Codon                  | 99                  |                     | 271                  | 33                  | 139        | 166                                     | 9/                  | 58                 |
| 3' NT<br>of<br>Clone<br>Seq.                | 3599                | 2496                | 1677                 | 1699                | 635        | 1752                                    | 1669                | 795                |
| 5' NT<br>of<br>Clone<br>Seq.                | 1                   | -                   | 1                    | 1                   | 78         | 52                                      | 1                   | 1                  |
| Total<br>NT<br>Seq.                         | 3599                | 2924                | 1677                 | 1699                | 637        | 1752                                    | 6991                | 795                |
| SEQ NI<br>NO ID                             | 396                 | 397                 | 256                  | 257                 | 258        | 259                                     | 260                 | 261                |
| Vector                                      | pCMVSport<br>3.0    | pCMVSport<br>3.0    | pCMVSport<br>3.0     | pCMVSport<br>3.0    | Uni-ZAP XR | Uni-ZAP XR                              | pCMVSport<br>2.0    | Uni-ZAP XR         |
| ATCCTM Deposit No:Z and Date                | PTA-868<br>10/26/99 | PTA-868<br>10/26/99 | PTA-1543<br>03/21/00 | PTA-499<br>08/11/99 | 209138     | 97922<br>03/07/97<br>209070<br>05/22/97 | PTA-848<br>10/13/99 | 209852<br>05/07/98 |
| cDNA<br>Clone ID                            | HWBEM18             | HWBEM18             | HWBFX31              | HWHGZ51             | HWTBK81    | HAGAI85                                 | HOFOC33             | HSDEZ20            |
| Gene<br>No.                                 | 245                 | 245                 | 246                  | 247                 | 248        | 249                                     | 250                 | 251                |

## Table 1B (Comprised of Tables 1B.1 and 1B.2)

10082] The first column in Table 1B.1 and Table 1B.2 provides the gene number in the application corresponding to the clone identifier. The second column in Table 1B.1 and Table 1B.2 provides a unique "Clone ID." for the cDNA clone related to each contig sequence disclosed in Table 1B.1 and Table 1B.2. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO.X as determined by directly sequencing the referenced clone. The referenced clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length DNA can be obtained by methods described elsewhere herein. The third column in Table 1B.1 and Table 1B.2 provides a unique "Contig ID" identification for each contig sequence. The fourth column in Table 1B.1 and Table 1B.2 provides the "SEQ ID NO." identifier for each of the contig polypucleotide sequences disclosed in Table 1B.

## Table 1B.1

[0083] The fifth column in Table 1B.1, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1B.1, column 6, as SEQ ID NO:Y. Where the nucleotide position number "To" is lower than the nucleotide position number "From", the preferred ORF is the reverse complement of the referenced polynucleotide sequence. The sixth column in Table 1B.1 provides the corresponding SEO ID NO:Y for the polypeptide sequence encoded by the preferred ORF delineated in column 5. In one embodiment, the invention provides an amino acid sequence comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by "ORF (From-To)". Also provided are polynucleotides encoding such amino acid sequences and the complementary strand thereto. Column 7 in Table 1B.1 lists residues comprising epitopes contained in the polypeptides encoded by the preferred ORF (SEQ ID NO:Y), as predicted using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, at least one, two, three, four, five or more of the predicted epitopes as described in Table 1B. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly.

[0084] Column 8 in Table [1B.1 provides a chromosomal map location for certain polynucleotides of the invention. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Each sequence in the UniGene database is assigned to a "cluster"; all of the ESTs, cDNAs, and STSs in a cluster are believed to be derived from a single gene. Chromosomal mapping data is often available for one or more sequence(s) in a UniGene cluster; this data (if consistent) is then applied to the cluster as a whole. Thus, it is possible to infer the chromosomal location of a new polynucleotide sequence by determining its identity with a mapped UniGene cluster.

[9085] A modified version of the computer program BLASTR (Altshul, et al., J. Mol. Biol. 215-403-410 (1990), and Gish, and States, Nat. Genet. 3:266-272) (1993) was used to search the UniGene database for EST or cDNA sequences that contain exact or near-exact matches to a polynucleotide sequence of the invention (the 'Query'). A sequence from the UniGene database (the 'Subject') was said to be an exact match if it contained a segment of 50 nucleotides in length such that 48 of those nucleotides were in the same order as found in the Query sequence. If all of the matches that met this criteria were in the same UniGene cluster, and mapping data was available for this cluster, it is indicated in Table 1B under the heading "Cytologic Band". Where a cluster had been further localized to a distinct cytologic band, that band is disclosed; where no banding information was available, but the gene had been localized to a single chromosome, the chromosome is disclosed.

[0086] Once a presumptive chromosomal location was determined for a polynucleotide of the invention, an associated disease locus was identified by comparison with a database of diseases which have been experimentally associated with genetic loci. The database used was the Morbid Map, derived from OMIMT<sup>M</sup> and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MI)) 2000;. If the putative chromosomal location of a polynucleotide of the invention (Query sequence) was associated with a disease in the Morbid Map database, an OMIM reference identification number was noted in column 9, Table 1B.1, labelled "OMIM Disease Reference(s). Table 5 is a key to the OMIM reference identification numbers (column 1), and provides a description of the associated disease in Column 2.

Table 1B.2

Column 5, in Table 1B.2, provides an expression profile and library code:count for each of the [0087] contig sequences (SEO ID NO:X) disclosed in Table 1B, which can routinely be combined with the information provided in Table 4 and used to determine the tissues, cells, and/or cell line libraries which predominantly express the polynucleotides of the invention. The first number in Table 1B.2, column 5 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. The second number in column 5 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence was identified in the corresponding tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array, cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of 33P dCTP, using oligo (dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which

show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

| t Band Disease ary Reference(s):                                         | 562:<br>00:<br>03:<br>03:<br>03:<br>771:<br>771:<br>744:<br>663:<br>663:<br>663:<br>744:<br>744:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |           | 803:                       |
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| Tissue Distribution Library code: count (see Table IV for Library Codes) | 80414 5, 98422, 7, 10662, 80414 5, 90442, 7, 10662, 1, 10734, 4, 10814, 6, 10734, 3, 10866, 1, 10734, 3, 10866, 1, 10734, 3, 10866, 1, 10734, 3, 10866, 1, 10734, 3, 10862, 1, 10862, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 10874, 1, 1 |           | L0805: 4, H0559: 3, L0803: |
| Predicted Epitopes                                                       | Arg-74 to Gla-168.<br>Gla-146 to Gla-168.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |           | Arg-5 to Pro-12.           |
| SEQ<br>BOS A                                                             | 405                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 959       | 406                        |
| ORF<br>(From-To)                                                         | 157 - 777                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 157 - 312 | 389 - 733                  |
| SEQ ID<br>NO: X                                                          | =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 262       | 12                         |
| Contig<br>ID:                                                            | 884134                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 745366    | 543259                     |
| Gene cDNA Clone ID Contig                                                | HZCBURS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | H2CBU83   | H6EDC19                    |
| Gene<br>No:                                                              | -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |           | 2                          |

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| 1, S0026: 1, H0543: 1 and<br>H0423: 1. |                                        | L0439, 5, 80051; 3, 80007;<br>2, 80422; L0438; 2,<br>H0171; 1, 80360; 1, H0411;<br>1, H0431; 1, 8000; 1,<br>H0569; 1, 80388; 1, H0163;<br>1, H0400; 1, L0805; 1, 80126; 1, 80406; 1,<br>L0742; 1, L0744; 1, L0747;<br>1, L0779; 1 and L0738; 1, | H0599: 1 | 1,005.5, 1,005.5, 3,04.6, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04.5, 5,04 |
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|                                        | Leu-31 to Phe-38,<br>Glu-47 to Trp-52. | Gly-49 to Ser-54,<br>Lys-61 to Arg-68.                                                                                                                                                                                                          |          | Assa-27 to tea-47,<br>Asp-93 to Lys-102,<br>Asp-93 to Lys-102,<br>Ass-107 to Lys-102,<br>Met.129 to Glu-41,<br>Glu-184, Glu-185,<br>Glu-33 to Leu-403,<br>Glu-423 to Gly-429,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                        | 859                                    | 411                                                                                                                                                                                                                                             | 412      | 6.14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                        | 52 - 405                               | 429 - 704                                                                                                                                                                                                                                       | 93 - 245 | 128 - 1468                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                        | 264                                    | 17                                                                                                                                                                                                                                              | 18       | <u>6</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                        | 543617                                 | 704425                                                                                                                                                                                                                                          | 635412   | 422672                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                        | HAGDS35                                | HAGF162                                                                                                                                                                                                                                         | 91ECHVH  | HAICP19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                        |                                        | 7                                                                                                                                                                                                                                               | 8        | 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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| and H0542: 1. | H0265:1, H0159:1, S0132:<br>, H0574:1, H0075:1,<br>10042:1, H0509:1 and<br>S0434:1.                        | SAGOR, 2, 1406 19.2, 50438. 1,0803.2, 140845. 1,0803.2, 1,08045. 1,0033.1,8003.1,14064. 1,0033.1,8003.1,14064. 1,0033.1,8003.1,14064. 1,0038.1,14064. 1,0038.1,14063. 1,0038.1,14063. 1,0038.1,14063. 1,0038.1,14063. |           | S0004.4. T000.4. H0560.<br>L0794.4. S0402. 1. H0560.<br>L0497.2. H0605.2. H0605.<br>S0212.2. H0619.2. H0612.<br>L16049.2. L0766.2. L0761.<br>L16049.2. L0766.2. L0761.<br>L16056.1. L0791.<br>L16059.1. L0792.<br>L16059.1. L0793.<br>L16059.1. L0793.<br>L16059.1. L0799.1. L0793.<br>L16059.1. L0799.1. L0799.<br>L16059.1. L0799.1. L0799.<br>L16059.1. L0799.1. L0799.1. L0799.<br>L16059.1. L0799.1. L0799.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| l and         | H0265:<br>1, H0574<br>T0042: 1<br>S0434: 1                                                                 | S0408:<br>2, L0803<br>1, H073<br>1, H073<br>1, H0623:<br>1, H0629:<br>1, L076e<br>1, L076e<br>1, H0555:<br>1, H0555:<br>1, H0555:                                                                                     |           | S004<br>4, L07<br>2, C0455<br>2, H0492<br>2, H04<br>2, H05<br>1, H05 |
|               | Glu-28 to Gly-45,<br>Ser-63 to Gly-69,<br>Gln-96 to Trp-104,<br>Gly-112 to Pro-117,<br>Arg-121 to Pro-128. | Pro-186 to Tyr-196,<br>Leu-294 to Leu-380,<br>Sen-380 to Thr-385,<br>Thr-486 to Ser-499,<br>Phe-513 to Ser-522.                                                                                                       |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|               | 414                                                                                                        | 415                                                                                                                                                                                                                   | 629       | 416                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|               | 274 - 693                                                                                                  | 109 - 1797                                                                                                                                                                                                            | 120 - 629 | 262 - 423                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|               | 20                                                                                                         | 21                                                                                                                                                                                                                    | 265       | 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|               | 676933                                                                                                     | 1352364                                                                                                                                                                                                               | 872551    | 918869                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|               | HAIFL18                                                                                                    | HAJAN23                                                                                                                                                                                                               | HAJAN23   | нллвкө                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|               | 01                                                                                                         | =                                                                                                                                                                                                                     |           | 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| L0748: 1, S0436: 1, L0591:<br>1, H0542: 1, S0424: 1 and<br>H0677: 1. | 1,0748; 0,1074-9; 0,1076-8; 10439; 1,7,1089; 6,10642-4; 1,7,1089; 6,10642-4; 1,7,1089; 6,10642-4; 1,0704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,10704-4,107 |
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|                                                                      | (Gp-93) to Abs. (165, Gp-93) to Abs. (165, Gp-93) to Abs. (165, Gp-93) to Abs. (165, Gp-93) to Gp-93) to Gp-93  |
|                                                                      | 714                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                      | 1495 - 2757                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                      | 23                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                      | 905695                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                      | HAMFEIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 199                                                             | 419                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 40 - 651                                                        | 252 - 377                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 267                                                             | 25                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 748223                                                          | 656755                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HAMGR28                                                         | HAPBS03                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                 | 15                                                                                                                                                                                                                       |

| 12. L0775. 2, L0669. 2, L0665. 2, L0665. 2, L0665. 2, L0665. 2, L0665. 2, L0787. 2, L0665. 2, L0787. 1, L0787. 1, L0367. 1, L0787. 1, L0367. 1, L0787. 1, L0367. 1, L0787. 1, L0 | L0794; 8, H0556; 5, S0414;<br>4, L0769; 4, L0779; 4,<br>H0031; 3, H0644; 3, L080;<br>5, S0216; 3, H0547; 3,<br>S0328; 3, H0422; 3, H0265;<br>2, H0200; 2, H0484; 2,<br>S0360; 2, S0410; 2, H0688;<br>2, H0617; 2, H0634; 2, |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 420                                                                                                                                                                                                                         |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 26                                                                                                                                                                                                                          |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 16                                                                                                                                                                                                                          |

| (1941): 2, L0763; 2, L0655; 1, L0655; 2, L0655; 2, L0655; 2, L0655; 2, L0655; 2, L0655; 2, L0651; 2, L0751; 2, L0751; 2, L0751; 2, L0751; 2, L0751; 2, L0752; 2, 1041; 2, L0752; 2, 1041; 2, L0752; 2, 1041; 2, L0452; 1, L0452; 1, L0652; 1, L0653; 1, L0654; 1, L0653; 1, L0654; 1, L0653; 1, L0776; 1 | 85406.2.5.10736.3.10777.<br>1.0749.3.10779.<br>1.0749.2.10770.<br>1.0749.2.10770.<br>1.0747.2.10780.<br>1.0747.2.10780.<br>1.0747.2.10780.<br>1.0747.1.10842.1.1079.<br>1.0015.1.10842.1.1079.<br>1.0015.1.10842.1.10811.<br>1.0015.1.10831.1.10843.1.10841.1.10861.<br>1.0015.1.10831.1.10843.1.10841.1.10861.<br>1.0015.1.10831.1.10841.1.10861.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| 8 7 8 7 8 7 8 7 8 7 8 7 9 7 9 7 9 7 9 7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Gla-23 to Asp-30,   St.     Lys-66 to Cys-87;   41,     Lys-66 to Cys-87;   41,     Lys-67 to Cys-87;   11,     Lys-87 to Cys-87;   11, |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 421 Glin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 251 - 817                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | НАРОМ49 769555                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| 1, H0593: 1, S0380: 1,<br>S0027: 1, L0748: 1, L0439:<br>1, L0756: 1, L0755: 1,<br>L0758: 1, L0485: 1, H0542: 1<br>and H0423: 1. |                                                              | H0575: 1  | L0534;4,L0562;3,L0527;<br>3,H0254;2,8045;2,<br>401.66;2,L0589;2,H0255;<br>1,H0402;1,L0539;1,H0615;<br>1,H0598;1,H0615;<br>1,H0598;1,L0493;1,L0666;<br>1,80052;1,H0539;1,<br>1,0747;1,L0752;1,and | H0294: 2          |                   | H0410: 1, H0530: 1, H0328:<br>1, L0455: 1 and L0740: 1. | Supta, 13, 10747; 7, 80410<br>KHO67; 5, 10777; 8 10410<br>KHO67; 5, 10777; 8 10410<br>KHO62; 3, 10404; 1, 10408; 1, 10408; 1, 10408; 1, 10408; 1, 10408; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; 1, 10709; |
|                                                                                                                                 | Met-1 to Cys-21,<br>Cys-41 to Asp-59,<br>Pro-104 to His-116. |           | lk-25 to Trp-30.                                                                                                                                                                                 | Asn-34 to Lys-42. | Ala-17 to Lys-23. |                                                         | Pro-51 to Asp-56,<br>(190-58 to The 105,<br>Val-132 to Ata-138,<br>Pro-229 to Lea-240.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                 | 662                                                          | 422       | 423                                                                                                                                                                                              | 424               | 699               | 425                                                     | 426                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                 | 448 - 816                                                    | 385 - 807 | 252 - 446                                                                                                                                                                                        | 253 - 399         | 575 - 643         | 695 - 066                                               | 124-843                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                 | 268                                                          | 78        | 29                                                                                                                                                                                               | 30                | 569               | 31                                                      | 32                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                 | 722386                                                       | 834358    | 635514                                                                                                                                                                                           | 600689            | 383592            | 581129                                                  | 1352289                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                 | HAPOM49                                                      | HAPUC89   | HATBR65                                                                                                                                                                                          | HAUAI83           | HAUAI83           | HBAMB15                                                 | HBGBA69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                 |                                                              | 81        | 61                                                                                                                                                                                               | 20                |                   | 21                                                      | 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| 1, 1552. 1, 10666. 2, 16666. 2, 16666. 2, 16661. 2, 12011. 3, 10261. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 10361. 3, 1036 | 1, S0260: 1, H0445: 1,<br>S0434: 1, S0196: 1, H0423: 1<br>and H0506: 1. |                   |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                         | Thr-52 to Gly-57. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Ş                                                                       | 664               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                         | 62 - 244          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                         | 270               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                         | 709658            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                         | HBGBA69           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                         |                   |

|                            | _                     | _                         | _                                                | _                   | _                          | _                     | _                          | _                   | _                         | _                     | _                          | _                     | _         | _                          | _                   | _                            | _                         | _                     | _                         | _                     | _                          | _                     | _                          | _                  | _                          | _                     | _                          | _                  | _                          | _                     | _                          | _                     | _                         | _                     | _                          |                                                     |
|----------------------------|-----------------------|---------------------------|--------------------------------------------------|---------------------|----------------------------|-----------------------|----------------------------|---------------------|---------------------------|-----------------------|----------------------------|-----------------------|-----------|----------------------------|---------------------|------------------------------|---------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|--------------------|----------------------------|-----------------------|----------------------------|--------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------------------------------------|
|                            |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| H                          |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
|                            |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| 0486:                      |                       | 748:                      | .500                                             |                     | 176:                       |                       | 1529:                      |                     | 749:                      |                       | 497:                       |                       | 42: 2,    | 306:                       |                     | 127: 2.                      | 731:                      |                       | 352:                      |                       | 365:                       |                       | 305:                       |                    | .946                       |                       | 333:                       |                    | 318:                       |                       | 545:                       |                       | .889                      |                       | 182:                       | 551:                                                |
| 0114: 5, H                 | 30344: 5,             | 436: 5, L0                | 10255: 4,                                        | F0049: 3.           | 356: 3, SO                 | H0271: 3,             | 087: 3, H(                 | .0766: 3,           | 747: 3, LO                | T0740: 2,             | 376: 2, HO                 | T0616: 2,             | 44: 2, SO | 378: 2, LO                 | 10658: 2,           | 14: 2. SO                    | 777: 2, LO                | .0588: 2,             | 124: 2, L2                | F0002: 1,             | 717: 1, L2                 | .2919: 1,             | 402: 1, H(                 | 10580: 1,          | 728: 1, S0                 | 30278: 1,             | 586: 1, H(                 | .0021: 1,          | 048: 1, HC                 | T0263: 1,             | 530: 1, H(                 | 30388: 1,             | 334: 1, H0                | 10424: 1,             | 628: 1, H(                 | 10090: 1,<br>063: 1, H(                             |
| H0617: 7, S0114: 5, H0486: | , H0069: 5, S0344: 5, | 0794: 5, H0436: 5, L0748: | , HO541: 4, HO255: 4,<br>0744: 4 C0436: 4 HO205: | H0294: 3. T0049: 3. | 10661: 3, S0356: 3, S0476: | , H0581: 3, H0271: 3, | 10038; 3, H0087; 3, H0529; | L0364: 3, L0766: 3, | 0126: 3, L0747: 3, L0749: | , H0423: 3, H0740: 2, | 10657; 2, S0376; 2, H0497; | , H0635: 2, H0616: 2, | 40:2, S01 | .0771: 2, L0378: 2, L0806: | L0518; 2, H0658; 2, | 0044; 2, S3014; 2, S0027; 2, | 0754: 2, L0777: 2, L0731: | . H0445; 2, L0588; 2, | 0599: 2, S0424: 2, L2852: | , H0556: 1, T0002: 1, | 10040: 1, H0717: 1, L2865: | , H0656: 1, L2919: 1, | .0381: 1, H0402: 1, H0305: | S0360: 1, H0580: 1 | 10722: 1, H0728: 1, S0046: | , H0747: 1, S0278: 1, | 10549: 1, H0586: 1, H0333: | T0060: 1, L0021: 1 | 10575: 1, T0048: 1, H0318: | , H0421: 1, H0263: 1, | 10597: 1, H0530: 1, H0545: | , H0041: 1, S0388: 1, | 10266: 1, S0334: 1, H0688 | , L0483: 1, H0424: 1, | 10644: 1, H0628: 1, H0182: | , H0316: 1, H0090: 1,<br>10591: 1, H0063: 1, H0551; |
| DH H                       | E ;                   | F07                       | E 6                                              | 3.0                 | H06                        | Э, н                  | H00                        | 3, 1                | SOI                       | 3, H                  | H06                        | 5, H                  | S04       | <u>1</u> 02                | 2.                  | 800                          | F02                       | 2, H                  | F02                       | 5<br>E                | 800                        | Η,                    | H03                        | 1, S               | H07                        | Η,                    | H05                        | 1, T               | HOS                        | 1, H                  | HOS                        | Н,П                   | H02                       | 1, L                  | 90 <u>H</u>                | 1, H                                                |
| a-33,                      | sp-82,                | a-97,                     | ys-125,<br>bo 125                                | er-185.             |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| Thr-19 to Ala-33           | Lcu-54 to Asp-82,     | Pro-89 to Ala-97,         | Pro-100 to Lys-125,<br>Cor 127 to Dbs 135        | Ser-180 to Ser-185. |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| 427                        |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| 125 - 679                  |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| 33                         |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| 1352412                    |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| HBGNU56                    |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |
| 23                         |                       |                           |                                                  |                     |                            |                       |                            |                     |                           |                       |                            |                       |           |                            |                     |                              |                           |                       |                           |                       |                            |                       |                            |                    |                            |                       |                            |                    |                            |                       |                            |                       |                           |                       |                            |                                                     |

| 426:<br>770:<br>800:<br>805:<br>856:<br>866:<br>690:<br>1406:<br>nd                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                         |                  | 0657:1                                                                                                           |                                        |
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| H0054: H0042: L<br>1000.1.H0280: L<br>0220: L1290: L<br>1076: L1290: L<br>1076: L1290: L<br>1076: L1290: L<br>1076: L1290: L<br>1080: L1077: L<br>1081: L1077: L<br>1082: L1077: L<br>1083: L1077: L<br>1083: L1089: L                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                         | 1.0440.1         | 200-92: 1 and 201-96: 1.<br>H0593: 2, H0617: 1, L0657:<br>and L0592: 1.                                          |                                        |
| H H 1054 1, H 1055                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                         | 1                | 20049; 1 and 20146; 1<br>H0593; 2, H0617; 1, I<br>and L0592; 1.                                                  |                                        |
| 1, H0266<br>H0100: 1<br>(1, L0769<br>L0761: 1<br>(1, L0658: 1<br>(1, L0658: 1<br>(1, L0658: 1<br>(1, L0658: 1<br>(1, L0658: 1<br>(1, L0698: 1<br>(1, L0798: 1<br>(1, L07 |                                                                                                                                                         | 0000             | H059;                                                                                                            |                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <sub>క్,క్</sub> ర్⊗                                                                                                                                    |                  | 2.4.6                                                                                                            |                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Ala-33,<br>Asp-82,<br>Ala-97,<br>Lys-12<br>Phe-13:<br>Ceu-16                                                                                            | Ser-31.          | Gly-37,<br>His-87,<br>Ala-10<br>Val-12                                                                           | Gly-37,<br>His-87,                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Thr-19 to Ala-33,<br>Leu-54 to Asp-82,<br>Pro-89 to Ala-97,<br>Pro-100 to Lys-125,<br>Ser-127 to Phe-135,<br>Gly-164 to Leu-169,<br>Cys-173 to Arg-178. | Arg-16 to Ser-31 | Ser-22 to Lys-27. Gly-32 to Gly-37, Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122, Lys-164 to Tyr-170 | Gly-32 to Gly-37,<br>Glu-78 to His-87, |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 999                                                                                                                                                     | 999              | 429                                                                                                              | 199                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 79 - 612                                                                                                                                                | 2-658            | 57 - 578                                                                                                         | 71 - 592                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | .67                                                                                                                                                     | 2-               | 57.                                                                                                              | 71.                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 271                                                                                                                                                     | 272              | 35                                                                                                               | 273                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1094642                                                                                                                                                 | 1050255          | 1352386                                                                                                          | 961712                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HBGNU56                                                                                                                                                 | HBGNU56          | HBINS58                                                                                                          | HBINS58                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                         | 7.0              | 25                                                                                                               |                                        |

|                                                                   |                                                                                      | H0255: 2, H0318: 2, H0341:<br>, L0519: 1, S0053: 1 and<br>.0748: 1. | H0318: 1 | L0766: 3 and H0188: 1. | H0052: 9, L0794: 6, L0758: | 5, L0659: 5, L0666: 4, | 3438: 4, S0126: 4, L0754: | I, L0779: 4, H0617: 3, | .0748: 3, L0751: 3, L0759: | , H0333: 2, H0013: 2, | I0150: 2, H0494: 2, L0761: | , L0641: 2, L0649: 2, | 0809: 2, L0519: 2, L0663: | , S0380: 2, L3832: 2, | 3439: 2, L0747: 2, L0749: | , H0685: 1, H0713: 1, | I0295: 1, H0341: 1, H0484: | , H0255: 1, H0638: 1, | 0358: 1, S0046: 1, S0476: 1, | 10393: 1, L3388: 1, H0261: | , S0222: 1, H0592: 1, | 10069: 1, H0253: 1, H0596: | , H0009: 1, H0178: 1, | 10081: 1, H0051: 1, H0266: | , H0428: 1, H0100: 1, | 0112: 1, L0639: 1, L5575: | , L3905: 1, L0662: 1, | 0766: 1, L0804: 1, L0651: | , L0655: 1, L0787: 1, | .0664: 1, L0665: 1, T0068: |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------|----------|------------------------|----------------------------|------------------------|---------------------------|------------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|------------------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|---------------------------|-----------------------|----------------------------|
| Tyr-102 to Ala-107,<br>Pro-115 to Val-122,<br>Lys-164 to Gln-171. | Gly-32 to Gly-37,<br>Glu-78 to His-87,<br>Tyr-102 to Ala-107,<br>Pro-115 to Val-122. |                                                                     |          |                        |                            |                        |                           | 4                      | _                          | 3                     | Gly-264 to Asp-272. H      | 2                     | <u> </u>                  | 2,                    | <u> </u>                  | 2                     | <u> </u>                   | -                     | <u>x</u>                     |                            | 1,                    | H                          | -                     | <u> </u>                   | 1,                    | <u>x</u>                  | 1,                    | 1                         | <u></u>               | 7                          |
|                                                                   | 899                                                                                  | 430                                                                 | 431      | 432                    | 433                        |                        |                           |                        |                            |                       |                            |                       |                           |                       |                           |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                           |                       |                           |                       |                            |
|                                                                   | 100 - 732                                                                            | 20 - 142                                                            | 87 - 227 | 77 - 262               | 166 - 1125                 |                        |                           |                        |                            |                       |                            |                       |                           |                       |                           |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                           |                       |                           |                       | _                          |
|                                                                   | 274                                                                                  | 36                                                                  | 37       | 38                     | 39                         |                        |                           |                        |                            |                       |                            |                       |                           |                       |                           |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                           |                       |                           |                       |                            |
|                                                                   | 892924                                                                               | 460392                                                              | 638410   | 526797                 | 634016                     |                        |                           |                        |                            |                       |                            |                       |                           |                       |                           |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                           |                       |                           |                       |                            |
|                                                                   | HBINS58                                                                              | HBJFU48                                                             | HBJLC01  | HBNAW17                | HCE2F54                    |                        |                           |                        |                            |                       |                            |                       |                           |                       |                           |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                           |                       |                           |                       |                            |
|                                                                   |                                                                                      | 26                                                                  | 27       | 28                     | 59                         |                        |                           |                        |                            |                       |                            |                       |                           |                       |                           |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                           |                       |                           |                       | 1                          |

| 1, H0672: 1, H0539: 1,<br>L0602: 1, S0406: 1, H0436:<br>1, H0478: 1, L0777: 1,<br>L0755: 1, H0422: 1 and<br>H0506: 1. | 1,0429-8, 110032-7, 10748, 20440-5, 10708-7, 10748, 20440-5, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708-4, 10708 |
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|                                                                                                                       | Lips-Stot Gib-T7, Gib-Gib-Gib-Gib-Gib-Gib-Gib-Gib-Gib-Gib-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                       | 4.54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                       | 165 - 1175                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                       | 04                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                       | 728432                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                       | HCE3G69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                       | 390                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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                                               | Lys-50 to Leu-69. | 10-70 to oxel-st,<br>Thr-14 to Gly-148,<br>Thr-14 to Gly-148,<br>Pa-197 to Gli-205,<br>Thr-12 to Gl-205,<br>Gli-242 to Bc-248,<br>Thr-265 to Leu-271.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| Met-I to Ala-8,<br>Ser-51 to Leu-G2,<br>Pro-70 to Lys-78,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Met-1 to Ala-8. | Tyr-30 to Scr-40.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| 12 - 281                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 5 - 274         | 10 - 168                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| HCEFB80                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HCEFB80         | HCENK38                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| H06(15.1,110039.1,110644:<br>1,15056.1,11013.1,1100009.1,1100009.1,110009.1,11013.1,110003.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110009.1,110 | H0052: 2, H0261: 1, H0271:<br>1 and S0458: 1. | H0423: 1 | L 078,6, L0794, \$3386, \$1, L0492, \$1, L0492, \$1, L0472, \$1, L0492, \$1, L0492, \$1, L0892, \$2, L0493, \$1, L0892, \$2, L0492, \$2, L0492, \$2, L0792, \$2, L0792, \$2, L0792, \$2, L0792, \$1, L0492, |
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|                                                                                                                                           |                                                                                                                 |                   |                        |                                                                                      |                                                                                                                                |             |                                  | 108725, 109480,<br>111250, 120700,<br>130130, 130130,                                      | 133171, 136836,<br>145981, 147141,                   | 147840, 164953,        | 277600, 600957,        | 601238, 601240,<br>601768, 601846.                      | 602018, 602216, | 602216, 602216,<br>602477, 605248 |                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------|------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------|----------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------|------------------------|---------------------------------------------------------|-----------------|-----------------------------------|------------------------------------------------|
|                                                                                                                                           | I                                                                                                               |                   |                        |                                                                                      |                                                                                                                                |             |                                  | 19p13.3                                                                                    |                                                      |                        |                        |                                                         |                 |                                   |                                                |
| 1, L0803: 1, L0804: 1,<br>L0805: 1, L0776: 1, L0438:<br>1, H0689: 1, H0659: 1,<br>H0658: 1, H0660: 1, H0666:<br>1, L0594: 1 and S0106: 1. | L0794; 3, L0764; 2, L0439;<br>2, H0052; 1, H0597; 1,<br>T0006; 1, L0766; 1, H0648;<br>1, S0330; 1 and L0753; 1. |                   | H0231: 1 and S0216: 1. | \$0356: 4, H0596: 2, H0032:<br>2, H0685: 1, \$0442: 1,<br>H0270: 1, H0156: 1, H0046: | I, M0022; 1, L0453; 1,<br>H0674; 1, S0440; 1, L0372;<br>1, L0364; 1, L0805; 1,<br>L0663: 1, S0374; 1, S0434; 1<br>and 10599; 1 |             | H0402: 1, H0779: 1 and L0747: 1. | L0789; 4, L0809; 2, L0759; 19p13.3<br>2, L0596; 2, H0306; 1,<br>H0402; 1, H0580; 1, H0550; | 1, H0370: 1, H0404: 1,<br>H0559: 1, H0486: 1, H0031: | 1, H0674: 1, H0135: 1, | 1, L0804: 1, L0805: 1, | L0515: 1, L0783: 1, H0672:<br>1, L0777: 1, H0444: 1 and | H0352: 1.       |                                   | L0752: 30, L0754: 17,<br>L0740: 16, H0521: 14, |
|                                                                                                                                           | Pro-71 to His-92.                                                                                               | Pro-71 to His-92. | Pro-26 to Asn-32.      |                                                                                      |                                                                                                                                |             |                                  |                                                                                            |                                                      |                        |                        |                                                         |                 |                                   |                                                |
|                                                                                                                                           | 141                                                                                                             | 671               | 442                    | 443                                                                                  |                                                                                                                                | 673         | 444                              | 445                                                                                        |                                                      |                        |                        |                                                         |                 |                                   | 446                                            |
|                                                                                                                                           | 21 - 401                                                                                                        | 124 - 507         | 218 - 349              | 381 - 389                                                                            |                                                                                                                                | 1702 - 1710 | 91 - 225                         | 557 - 700                                                                                  |                                                      |                        |                        |                                                         |                 |                                   | 19 - 318                                       |
|                                                                                                                                           | 47                                                                                                              | 277               | 8/7                    | 49                                                                                   |                                                                                                                                | 279         | 50                               | 51                                                                                         |                                                      |                        |                        |                                                         |                 |                                   | 52                                             |
|                                                                                                                                           | 6169101                                                                                                         | 863677            | 526413                 | 911924                                                                               |                                                                                                                                | 906285      | 847040                           | 550208                                                                                     |                                                      |                        |                        |                                                         |                 |                                   | 707833                                         |
|                                                                                                                                           | HCNDR47                                                                                                         | HCNDR47           | HCNSB61                | нсостоя                                                                              |                                                                                                                                | HCQCT05     | HCUGM86                          | нсимея                                                                                     |                                                      |                        |                        |                                                         |                 |                                   | HCWDS72                                        |
|                                                                                                                                           | 37                                                                                                              |                   | 38                     | 39                                                                                   |                                                                                                                                |             | 40                               | 41                                                                                         |                                                      |                        |                        |                                                         |                 |                                   | 42                                             |

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| L0439: 14, L0766: 12,<br>20003: 11, S0214: 11, L0777<br>10, S0002: 8, L0770: 8,<br>L0776: 8, L0748: 8, L0753:<br>8, S0540; 7, L0665: 7,<br>L0757: 7, T0067: 6, S0440:<br>6, L0666: 6, L0747: 6, | L0774: 5, L0751: 5, S0222:<br>4, H0872: 4, H0822:<br>L062.4, L0775: 4, H0547:<br>4, S0126: 4, S0380: 4, L0750<br>4, L0758: 4, S0436: 4,<br>L0362: 4, H0638: 3, H0580:<br>5, H094: 5, S0422: 3,<br>L0583: 5, S0422: 3,<br>L0583: 5, S0422: 3,<br>L0583: 5, S0422: 3, | 5, H00.22, 1, H05.53, 1, L03.64, 2, L03.65, 3, L07.66, 3, L07.66, 3, L07.66, 3, L07.66, 3, L07.66, 3, L07.66, 2, L03.67, | H091.2, L0620.2, L10531.2, L0620.2, L10531.2, L0620.2, L0632.2, L10632.2, L             |
|                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 447                    | 448                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 37 - 159               | 270 - 407                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 53                     | 54                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 553621                 | 639037                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCWKC15                | HCWUM50                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 43                     | 44                                                                                                                                     |

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| Leu-30 to Gly-38, Arg-67 to Val-72, Val-76 to Ala-89, Pro-118 to Arg-123, Gly-129 to Ala-136, Leu-138 to Arg-146, | Leu-30 to Gly-38, Arg-67 to Val-72, Val-76 to Ala-89, Pro-118 to Arg-123, Gly-129 to Ala-146, Leu-138 to Arg-146, | (Gla-3) or Trp-4y, (Gla-3) or Trp-4y, (Gla-3) or Arg-21, (Il-207) ox Arg-21, Val-41 or Gla-19, Val-41 or Gla-19, Val-41 or Lou-47, (Il-207) or Lou-47, Met-87 or Gla-8y, Met-87 or Gla-8y, (Il-21) or Gla-8 | Gln-33 to Trp-49,<br>Gly-161 to Gly-172,<br>Ile-207 to Arg-212,<br>Asn-414 to Val-419,<br>Val-436 to Gly-441,<br>Lys-467 to Leu-478, |
| 449                                                                                                               | 674                                                                                                               | 450                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 675                                                                                                                                  |
| 33 - 473                                                                                                          | 28 - 468                                                                                                          | 259 - 3084                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 69 - 2894                                                                                                                            |
| 55                                                                                                                | 280                                                                                                               | 56                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 281                                                                                                                                  |
| 1301517                                                                                                           | 748225                                                                                                            | 1062783                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 866429                                                                                                                               |
| HDABR72                                                                                                           | HDABR72                                                                                                           | <b>ПРВВА28</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HDPBA28                                                                                                                              |
| 45                                                                                                                |                                                                                                                   | 46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                      |

|                                                                                                                                                               | L0769: 6, S0106: 2, S0110:<br>1, H0441: 1, S0049: 1,<br>1,0022: 1, S0049: 1,<br>1, L0384: 1, L0773:<br>1, L0384: 1, L0789: 1,<br>1, L0741: 1, L0758: 1 |                                                                                                                |          | HISSON 2, L0766: 2, S0114: 1, S0218: 1, S0422-1, S0045: 1, H0333-1, H0013: 1, 1, S0324-1, H0031: 1, 2, S6028: 1, H0266: 1, 2, S6028: 1, H0266: 1, 2, S6028: 1, H0261: 1, 3, S6028: 1, H0261: 1, H0 | L0731: 8, L0439: 6, L0659: 15, L0431: 8, L0444: 4, L0744: 4, L0774: 4, L0774: 4, L0774: 4, L0774: 1, L0023: 1, L0665: 1, L0675: 1, L0670: 2, L0747: 1, L0747                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Phe-497 to Ser-508,<br>Met-550 to Gly-560,<br>Glu-688 to Thr-697,<br>Ite-711 to Gly-720,<br>Ala-747 to Gly-729,<br>Ala-747 to Gly-729,<br>Ser-795 to Gli-800. |                                                                                                                                                        | Ala-12 to Glu-27, Pro-35 to Ser-43, Pro-35 to Ser-70, Ser-92 to Val-98, Pro-166 to The-175, Ser-23 to The-246, |          | Tyr-33 to Lys-38. [100] 1, 800 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 1, 100 | IR-4 to GIs-10 1.07;<br>Gis-38 to Asp-64 1.07;<br>Gis-38 to Asp-64 1.07;<br>Hozza 1.07<br>Hozza 1.07<br>Sis-107<br>Corp. 1.07<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lory-00<br>Lo |
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|                                                                                                                                                               | 37 - 984                                                                                                                                               | 103 - 915                                                                                                      | 51 - 464 | 131 - 286                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 35 - 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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 829                                                                                                         | 629                                   |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 284                                                                                                         | 285                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 847045                                                                                                      | 897484                                |
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|                    |                     | H0521: 2, H0445: 2, H0394:<br>1, H0747: 1, H0581: 1,<br>L0761: 1 and L0750: 1. | I IIIO221, 3.0222, 16.2<br>2, H0244, 2, H0265; 1.<br>H07281, 19007; 1, H0208; 1, H0508; 1, H0092; 1, H | H0521: 1                             | LURON, 4. HUG7.3, HUG7.3, HUG7.3, LUG94.5, LUG7.2, LUG7.2, LUG7.2, LUG7.2, LUG7.2, LUG7.2, LUG7.3, LUG |                   | H0522: 2 and L0055: 1. | S0474: 29, L0766: 11,<br>H0521: 10, L0803: 7, L0748:<br>6, L0717: 5, L0759: 5, |
| Day 100 to Mar 100 | Pro-113 to Pro-118. | Pro-22 to His-33,<br>Ser-42 to Trp-48.                                         | Cys-63 to Ser-71.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Gly-2 to Glu-7,<br>Arg-27 to Gly-34. | Arg-15 to Valt-22.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Pro-41 to Ala-55. | Ala-107 to Scr-112.    | Lys-30 to Thr-35.                                                              |
|                    |                     | 454                                                                            | 455                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 456                                  | 457                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 089               | 458                    | 459                                                                            |
|                    |                     | 182 - 343                                                                      | 8 - 271                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 245 - 367                            | 59 - 1633                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 259 - 438         | 15 - 1469              | 159 - 527                                                                      |
|                    |                     | 09                                                                             | 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 62                                   | 63                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 286               | 64                     | 59                                                                             |
|                    |                     | 460682                                                                         | 771583                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 460679                               | 879325                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 603517            | 637586                 | 731863                                                                         |
|                    |                     | HDPC025                                                                        | HDPGT01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HDPHI51                              | НЭРЈМЗ0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HDPJM30           | HDPND46                | HDPOJ08                                                                        |
|                    |                     | 20                                                                             | 31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 52                                   | 83                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   | 54                     | 22                                                                             |

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| S0003: 4, L3832: 4, H0663: | .0770: 3, L0771: 3, L0804: | , L2439; 3, H0522; 3,<br>.0731; 3, S0436; 3, H0486; | , S0426: 2, L0805: 2, | .0659: 2, L2260: 2, S0126: | , S0406; 2, L0/49; 2, | .0/55: 2, L0/5/: 2, L0/58:<br>L0590: 2, S0026: 2 | 10716: 1. H0341: 1. S0212: | L0481: 1, S0444: 1, S0360: | L3649: 1, H0637: 1, | 10580: 1, H0734: 1, H0749: | L3092: 1, H0619: 1, | .3388: 1, H0586: 1, H0574: | , H0427: 1, L0021: 1, | 10575: 1, H0318: 1, H0545: | , H0024: 1, H0373: 1, | 0071: 1, H0179: 1, S0214: | , H0428: 1, H0674: 1, | 10591: 1, H0616: 1, H0488: | , H0494: 1, S0438: 1, | ,0440: 1, H0647: 1, S0142: | , UNKWN: 1, L0369: 1, | .0763: 1, L0769: 1, L0646: | L0648: 1, L0662: 1, | .0650: 1, L0775: 1, L0653: | , L0776: 1, L0656: 1, | .0782: 1, L0809: 1, L0519: | , S0052: 1, L2657: 1, | 10144: 1, L3823: 1, H0520: | , H0547: 1, H0660: 1, | 0380: 1, L0742: 1, L0439: | , L0750: 1, L0777: 1, | 30031: 1, H0445: 1, S0434: | , H0665: 1, H0667: 1, | 30194: 1, S0276: 1 and |           |
| S0003; 4,                  | L0770: 3,                  | 3, L2439:<br>L0731: 3                               | 2, S0426:             | L0659: 2,                  | 2, 50406:             | LU/55: 2,<br>2 T.0590:                           | H0716: 1                   | 1, L0481:                  | 1, L3649:           | H0580: 1.                  | 1, L3092:           | L3388: 1,                  | 1, H0427              | H0575: 1.                  | 1, H0024              | H0071: 1.                 | 1, H0428              | H0591: 1                   | 1, H0494              | S0440: 1,                  | I, UNKW               | L0763: 1,                  | 1, L0648:           | L0650: 1,                  | 1, L0776:             | L0782: 1,                  | 1, S0052:             | H0144: 1,                  | 1, H0547.             | S0380: 1,                 | 1, L0750:             | 80031:1,                   | 1, H0665              | S0194: 1,              | S0458: 1. |
|                            |                            |                                                     |                       |                            |                       |                                                  |                            |                            |                     |                            |                     |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                        | _         |
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|                                                                                                                            |           | 01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |           |             |                   |                                                                                |                                      |
| H0542: 4, S0418: 3, H0543: 3, S0038: 2, H0341: 1, L0018: 1, H0069: 1, H0090: 1, H0056: 1, H0494: 1, H0522: 1 and H0423: 1. |           | 1,006-3, 1,007-3, 1,006-6, 10, 2,007-3, 1,006-6, 10, 2,007-2, 2,006-2, 2,006-2, 2,006-2, 2,006-2, 2,006-2, 2,006-2, 2,006-2, 2,006-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2,007-2, 2 |           |             |                   | L0804: 2, H0521: 2, L0021:<br>1, H0617: 1, H0623: 1,<br>L0648: 1 and L0665: 1. |                                      |
|                                                                                                                            |           | Lys-23 to Lys-31. Ala-38 to Ser-43.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |           |             | Lys-57 to Gly-64. | Met-1 to Trp-6,<br>Leu-22 to Thr-27,<br>Pro-44 to Thr-63.                      | Met-1 to Trp-6,<br>Leu-22 to Thr-27, |
| 460                                                                                                                        | 189       | 461                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 682       | 683         | 684               | 462                                                                            | 989                                  |
| 127 - 267                                                                                                                  | 117 - 257 | 123 - 333                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 116 - 307 | 1525 - 1566 | 345 - 665         | 158 - 430                                                                      | 153 - 536                            |
| 99                                                                                                                         | 287       | 1.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 288       | 289         | 290               | 89                                                                             | 291                                  |
| 1037893                                                                                                                    | 895711    | 1043263                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 903816    | 905414      | 732097            | 1309174                                                                        | 1040056                              |
| HDPPN86                                                                                                                    | HDPPN86   | HDPSB18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HDPSB18   | HDPSB18     | HDPSB18           | HDPSH53                                                                        | HDPSH53                              |
| 95                                                                                                                         |           | 57                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |           |             |                   | 28                                                                             |                                      |

|                                                                                     |                                      | 1,079-6, 10751-5, 10722-5, 10722-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 10721-5, 107 |                   | L (10740; R, 10662; 3, 10659;<br>3, 10663; 3, 80422; 2,<br>10666; 3, 10439;<br>2, 10779; 2, 10417;<br>1, 1079; 1, 1075; 1, 1074;<br>1, 1079; 1, 10794; 1, 10794;<br>1, 1079; 1, 10794; 1, 10794;<br>1, 10797; 1, 10794; 1, 10794;<br>1, 10797; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1, 10794; 1 |
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| Pro-44 to Gly-58,<br>Ala-61 to Glu-74,<br>Pro-99 to Gly-111,<br>Cys-121 to Ser-127. | Met-1 to Trp-6,<br>Leu-22 to Thr-27. | (Gla-75 to Cys-80,<br>(Gla-11 to Ala-11)4,<br>(Gla-11 to Ala-11)4,<br>Ass-250 to Trp-240,<br>Gla-269 to Arg-274,<br>Pro-279 to Ala-286,<br>Ass-322 to Cys-28,<br>Ass-322 to Lou-367,<br>Lou-490 to Arg-497,<br>(Gla-556 to Lou-567,<br>Gla-556 to Lou-567,<br>Gla-556 to Lou-561,<br>(Gla-556 to Lou-561,<br>(Gla-556 to Lou-561,<br>(Gla-556 to Lou-561,<br>(Gla-556 to Lou-561,<br>(Gla-556 to Lou-561,<br>(Gla-556 to Lou-561,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Gln-75 to Cys-80. | Pro-29 to Lys-37.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                     | 989                                  | 463                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 687               | 464                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                     | 212 - 484                            | 184 - 2313                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 227 - 1153        | 2356 - 2499                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                     | 292                                  | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 293               | 70                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                     | 882768                               | 1352280                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 689129            | 744440                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                     | HDPSH53                              | HDPSP01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HDPSP01           | HDPSP54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                     |                                      | 59                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   | 09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| 1, L0438; 1, H0521; 1,<br>S0406; 1, L0754; 1, L0755; 1<br>and L0758; 1. |           | S0358: 4, S0280: 3, H0717: | 2, 1103 /0, 2, 1103 10, 2,<br>H05 56: 1 H07 16: 1 S0442: | 1. S0354: 1. S0476: 1. | H0393: 1, H0549: 1, H0586: | 1, T0082: 1, H0036: 1, | H0590: 1, H0596: 1, H0050: | 1, H0628: 1, H0264: 1, | H0494: 1, H0509: 1, L2257: | 1, L2654: 1, H0521: 1, | L0741: 1, L0439: 1, H0445: | 1, S0436: 1, L0605: 1, S0011: | 1 and H0665: 1. | H0677: 47, H0521: 14, | H0295: 3, H0587: 3, H0556: | 2, H0656: 2, H0638: 2, | H0411: 2, S0002: 2, L0766: | 2, L0776: 2, L0659: 2, | L0809: 2, H0670: 2, H0522: | 2, S0404: 2, L0743: 2, | L0744: 2, L0740: 2, L0731: | 2, S0134: 1, H0657: 1, | H0254: 1, S0476: 1, S0278: | 1, H0486: 1, H0575: 1, | H0606: 1, H0135: 1, H0561: | 1, S0438: 1, L0761: 1, | L0768: 1, L0655: 1, L2261: | 1, S0374: 1, H0690: 1, | H0435: 1, H0658: 1, H0696: | 1, H0678: 1, L0779: 1, | L0752: 1, H0445: 1, S0434: 1 | and S0436: 1. | S0278: 3, H0641: 3, S0142:<br>3, L0770: 3, H0521: 3, |
|-------------------------------------------------------------------------|-----------|----------------------------|----------------------------------------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|-------------------------------|-----------------|-----------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|------------------------------|---------------|------------------------------------------------------|
|                                                                         |           | Ser-28 to Phe-33,          | Us-48 to Val-54                                          | Pro-100 to Glu-105.    | Pro-107 to Glu-112,        | Leu-119 to Gln-125,    | Gly-335 to Leu-340,        | Ser-383 to Arg-396,    | Leu-417 to Lys-429,        | Asp-477 to Arg-482,    | Tyr-532 to Ser-540,        | Ile-542 to Asn-549.           |                 | Gly-12 to Tyr-26,     | Val-52 to Asp-59,          | Gln-88 to Asp-93,      | Arg-124 to Asn-129,        | His-193 to Arg-198,    | Gln-207 to Thr-213,        | Gln-338 to Arg-346,    | Ser-378 to Ala-384,        | Ser-413 to Arg-420,    | Ser-428 to Glu-434,        | His-443 to Ser 451,    | Glu-454 to Ser-461.        |                        |                            |                        |                            |                        |                              |               | Arg-23 to Gln-30,<br>Asp-37 to Asp-50,               |
|                                                                         | 889       | 465                        |                                                          |                        |                            |                        |                            |                        |                            |                        |                            |                               |                 | 466                   |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                              |               | 467                                                  |
|                                                                         | 179 - 343 | 90 - 1739                  |                                                          |                        |                            |                        |                            |                        |                            |                        |                            |                               |                 | 40 - 1440             |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                              |               | 117 - 1091                                           |
|                                                                         | 294       | 71                         |                                                          |                        |                            |                        |                            |                        |                            |                        |                            |                               |                 | 72                    |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                              |               | 73                                                   |
|                                                                         | 502472    | 866433                     |                                                          |                        |                            |                        |                            |                        |                            |                        |                            |                               |                 | 812737                |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                              |               | 630354                                               |
|                                                                         | HDPSP54   | HDPUH26                    |                                                          |                        |                            |                        |                            |                        |                            |                        |                            |                               |                 | HDPUW68               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                              |               | HDPWU34                                              |
|                                                                         |           | 19                         |                                                          |                        |                            |                        |                            |                        |                            |                        |                            |                               |                 | 62                    |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                              |               | 63                                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | _                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | _                 | $\neg$    | _           |                                                                                    |
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| H0271: 2 L0794: 2 L0748: 2 L0777: 2 L0994: 1 L0768: 1 L0776: 1 L07 |                                        | 1,045,4, 1,1065,1, 1,1065,2, 1,1065,2, 1,1065,2, 1,1066,1, 2,1079,3, 1,1066,1, 2,1079,3, 1,1066,1, 2,1077,2,1073,2,1073,2,1073,2,1073,2,1073,2,1073,2,1073,2,1073,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1,1070,2,1 |                   |           |             | H0553: 3, H0717: 2, H0486:<br>1, H0427: 1, H0081: 1,<br>H0014: 1, S0388: 1, H0112: |
| Glu-236 i Met-235,<br>Pro-271 to Arg-381,<br>Neg-306 to Ser-316,<br>Ser-318 to Gly-325.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Arg-25 to Ser-35,<br>Ser-37 to Gly-44. | Pro-39 to Trp 44.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Pro-39 to Trp-44. |           |             | Lys-5 to Lys-10,<br>Asn-33 to Lys-39,<br>Asp-48 to Lys-54,                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 689                                    | 88                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 069               | 169       | 692         | 469                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 111 - 245                              | 23 - 319                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 33 - 329          | 539 - 607 | 1190 - 1267 | 326 - 2149                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 295                                    | 47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 296               | 297       | 298         | 75                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 626102                                 | 879048                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 904768            | 895716    | 895715      | 785879                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPWU34                                | HDPXY01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HDPXY01           | HDPXY01   | HDPXY01     | 72ABLCIH                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                        | 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                   |           |             | 59                                                                                 |

| 1, H0030: 1, H0031: 1,<br>H0644: 1, H0488: 1, H0519:<br>1, L0759: 1, H0543: 1 and<br>H0506: 1.                | 1,068-8, 1,066-8; 1,066-8; 1,066-8; 1,066-8; 1,066-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,079-8; 1,0 |                                        |                   | L0439: 10, L0747: 9,<br>L0766; 8, L0770: 5, L0666;<br>4, L0734: 4, L0770: 5, L0669;<br>B, R0543: 3, L0483: 2,<br>H05443: 1, L0483: 2,<br>L0768: 2, L0662;<br>L0768: 2, L0662;<br>L0768: 2, L0768: 2, |
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| Pro-62 to Asp-67,<br>Asn-116 to Arg-123,<br>His-157 to Ala-162,<br>Val-242 to Lys-249,<br>Val-251 to Asp-264, | Ang-24to Ang-31,<br>Ilie-33 to Tip-41,<br>Met-43 to His-52.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Arg-24 to Arg-31,<br>Ite-33 to Gly-41. | Arg-24 to Arg-31. | Leu-9 to Tyr-15,<br>Asp-34 to Gln-46,<br>Pro-51 to Asp-57,<br>Gly-88 to Thr-104,<br>Thr-123 to Ser-128.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                               | 470                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 693                                    | 694               | 471                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                               | 132 - 302                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 148 - 471                              | 148 - 369         | 808 - 2427                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                               | 76                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 599                                    | 300               | 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                               | 1306984                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 879009                                 | 751707            | 619852                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 695               | 472                                                                                                                                                                   | 473                              | 474                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 515 - 757         | 99 - 398                                                                                                                                                              | 28 - 228                         | 91 - 309                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 301               | 78                                                                                                                                                                    | 62                               | 08                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 382025            | 740750                                                                                                                                                                | 570903                           | 847060                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HE2DE47           | HE2NVS7                                                                                                                                                               | не2РН36                          | HE8DS15                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                   | 89                                                                                                                                                                    | 69                               | 70                                                                                                                                                                      |

| (19657.2, 18009.2, 140031.<br>(2) (19657.2, 1009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009.2, 2009 | L0493-11, L0770-10, L0483-8, L2918-7, S0422, 6, L0483-8, L038-2, L0483-1, S0003-4, H078-4, S0003-4, H078-4, L0769-4, L0769-4, L0769-4, L0769-4, L0763-3, L0791-3, R0483-3, L0791-3, R0483-3, R04 |
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| HORS12_L10598<br>2_L08042_L10778.2_L10786.2_L10766.2_L10766.2_L10778.2_L10786.2_L10778.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10786.2_L10078.2_L10078.2_L10078.2_L10078.2_L10078.2_L10078.2_L10078.2_L10078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_L1078.2_ | 1, S0196: 1 and H0/21: 1.<br>H0615: 1 and H0144: 1 | H0570: 1, S0210: 1, L0792: 1, H0144: 1, L0595: 1, |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Pro-35 to Phe-41                                   | Gln-44 to Gly-51,<br>Gln-119 to Ala-124,          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 476                                                | 477                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 35 - 160                                           | 129 - 1193                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 82                                                 | 83                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 420063                                             | 1352337                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HE9HV07                                            | HE90W20                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 77                                                 | 73                                                |

| H0543; 1 and L0690; 1. |                   |                                          |           | S0358: 10, L0766: 4, S0196: | 4, H0556: 3, S0222: 3, | S0474: 3, H0436: 3, L0754: | 3, H0624; 2, H0255; 2, | H0735: 2. H0052: 2. L0769: | 2 L0806-2 H0521-2 | 10748-2 10740-2 10747- | 2. L0753: 2. L0758: 2. | L0362: 2. S0242: 2. H0423: | 2. H0717; 1. H0656; 1. | L2902: 1, S0030: 1, H0484: | S0420: 1. S0408: 1. | H0747: 1. H0393: 1. L3311: | 1, S0300: 1, S0278: 1, | H0549: 1, L0623: 1, H0635: | 1, H0194: 1, H0596: 1, | H0123: 1, H0375: 1, H0286: | 1, H0328: 1, H0622: 1, | H0038: 1, H0272: 1, S0344: | 1, S0422: 1, S0426: 1, L0771: | 1, L0768: 1, L0774: 1, | L0805: 1, L0776: 1, L0382: | 1, L0789: 1, L2262: 1, | H0144: 1, H0520: 1, S0126: | 1, H0689: 1, H0684: 1, | H0659: 1, H0658: 1, H0660: | 1, H0648: 1, H0672: 1, | S0380: 1, H0518: 1, H0696: | 1, S0027: 1, L0744: 1, | L0745: 1, L0780: 1, L0752: | 1, L0757: 1, S0436: 1, | L0592: 1, S0026: 1, H0542: | 1, H0543: 1 and H0422: 1. |
|------------------------|-------------------|------------------------------------------|-----------|-----------------------------|------------------------|----------------------------|------------------------|----------------------------|-------------------|------------------------|------------------------|----------------------------|------------------------|----------------------------|---------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|-------------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|---------------------------|
| Trp-209 to Ile-223.    | Gln-44 to Gly-51, | Gln-119 to Ala-124,<br>Tm-209 to Ile-223 |           |                             |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                           |
|                        | 969               |                                          | 269       | 478                         |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                           |
|                        | 136 - 1074        |                                          | 129 - 533 | 57 - 197                    |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                           |
|                        | 302               |                                          | 303       | 84                          |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                           |
|                        | 838598            |                                          | 834400    | 684254                      |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            | _                         |
|                        | HE90W20           |                                          | HE90W20   | HEEAG23                     |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                           |
|                        |                   |                                          |           | 74                          |                        |                            |                        |                            |                   |                        |                        |                            |                        |                            |                     |                            |                        |                            |                        |                            |                        |                            |                               |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                           |

| L0766: 3, L0777: 2, S0116:<br>1, S0376: 1, H0457: 1,<br>S0440: 1, L0771: 1, L0803:<br>1, L0804: 1, L0657: 1,<br>L0659: 1, H0525: 1, S0406: 1 | 0:1                                                                                                   |                                                                                | L0743. L0747. & L0758. L0764. L0763. L0764. L0765. L0662. L0662. L0769. L0769. L0769. L0769. L0769. L0769. L0662. L0662. L0777. 4 H070. L0777. 4 H070. L0777. 4 H070. L0777. 4 H070. L0777. L0777. L0769. L0779. L0779. L0769. L0779. L0769. L0779. L0769. L0779. L0769. L0773. L07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| L076<br>1, S03<br>S0440<br>1, L08<br>L0659<br>and L0                                                                                         | H0150: 1                                                                                              |                                                                                | L074<br>(0754)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(1751)<br>(175 |
|                                                                                                                                              | Met-1 to Pro-6,<br>Glu-58 to Cys-63,<br>Glu-65 to Gly-72,<br>Thr-74 to Asn-88,<br>Tyr-104 to Trp-109. | Mct-1 to Pro-6,<br>Glu-58 to Cys-63,<br>Glu-65 to Gly-72,<br>Thr-74 to Val-87. | Gla-36 to Lys-55.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 479                                                                                                                                          | 480                                                                                                   | 869                                                                            | 481                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 123 - 266                                                                                                                                    | 73 - 438                                                                                              | 67 - 435                                                                       | 53-316                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 88                                                                                                                                           | 98                                                                                                    | 304                                                                            | 87                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 603533                                                                                                                                       | 1307790                                                                                               | 570048                                                                         | 847073                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| HEOMQ63                                                                                                                                      | HEPAB80                                                                                               | HEPAB80                                                                        | HFABGI8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 75                                                                                                                                           | 76                                                                                                    |                                                                                | 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 88                                                      | 68                | 06                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 16                                     | 92                                                                                                               |
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| 3, 500-34;<br>5, 500-36;<br>5, 500-36;<br>5, 500-36;<br>1, 100-36;<br>1, 100 | S02.                                           |          |           | Gin-31 to Pro-39. H02<br>1, SO:<br>H062<br>and S                                                      | L08<br>1, H0<br>H006                                                          | Ala-19 to Lys-34. L04.                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 487                                            | 669      | 700       |                                                                                                       | 489                                                                           | 490                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 45 - 176                                       | 52 - 183 | 280 - 288 | 50 - 184                                                                                              | 110 - 271                                                                     | 158 - 262                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 93                                             | 305      | 306       | 94                                                                                                    | 95                                                                            | 96                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1011487                                        | 844413   | 874248    | 532060                                                                                                | 634743                                                                        | 545012                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | HFIIN69                                        | HEIIN69  | HFIIN69   | HFTUR10                                                                                               | HFKFG02                                                                       | HFTBM50                                                    |
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| 07592 L07712 2 L07712 2 CONTROLL OF CONTRO | H0088.2 8,0036.<br>10662.2 L0803.2, H071.<br>10662.2 L0803.2, H071.<br>10722.1, H0013.1, H0108.<br>10722.1, H0013.1, H0108.<br>10722.1, H0013.1, H0108.<br>10004.1, H013.1, S0051.<br>10004.1, H013.1, S0051.<br>10004.1, H013.1, S0051.<br>10004.1, L0003.1, L00003.1, L00003.1, L0003.1, L0003.1, L0003.1, L0003.1, L00003.1, L00003.1, L00003.1, L0003 | 2, 100-22, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, 2, 100-28, |
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| S0001: 1          | H0590: 2, S0282: 1, H0486:<br>H0421: 1 and H0594: 1. | H0257: 49, H0256: 15 and 80282: 1.     | LU784, 6, HU766, 6, LU665;<br>LU781, 6, HU578, 4, LU78, 6, LU784, 4, | H0351: 10, L0439: 4,<br>.0766: 3, L3255: 2, L2562: |
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| His-55 to His-67. |                                                      | Lys-23 to Lys-35,<br>Met-46 to Tyr-52. | . % % %<br>% % %<br>. %                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Ser-40 to Gly-45,<br>Leu-73 to Arg-80.             |
| 493               | 494                                                  | 495                                    | 496                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 497                                                |
| 247 - 450         | 98 - 241                                             | 44 - 220                               | 87 - 96 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 231 - 596                                          |
| 66                | 100                                                  | 101                                    | 102                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 103                                                |
| 609826            | 886102                                               | 634161                                 | 570262                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 566838                                             |
| HFXHK73           | HFXJX44                                              | HFXKY27                                | HGBH135                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HGLAF75                                            |
| 68                | 06                                                   | 16                                     | 26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 93                                                 |

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| 2, L0775: 2, L0666: 2,<br>L0789: 2, L0781: 2, L0785: 2, L0781: 2, L0781: 2, L0781: 2, L0781: 2, L0781: 1, L0486: 1, L0076: 1, L076: 1, L076: 1, L076: 1, L076: 1, L0776: | [10746 68422.5 180575.<br>2.19266.2 18028.2<br>1.1028.2 18076.2 10748.<br>1.1028.2 18076.1 18074.<br>1.10467.1 1.1041.<br>1.10467.1 1.1041.<br>1.10467.1 1.1057.<br>1.1002.1 1.1053.1 1.1055.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.1057.1 1.10 |                                                                                                         |             | H0341: 1 and H0542: 1. | H0543; 2, H0497; 1 and | H0625: 1.         | HU580: 1 and HU050: 1.                                                           | L0748: 9, H0620: 6, L0439:<br>6, L0766: 5, L0774: 5,<br>H0657: 4, L0758: 4, S0358: |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Sec-25 to Ata-30,<br>Arg-53 to Ata-30,<br>Arg-53 to Ata-64,<br>Glu-82 to Phe-93,<br>Sec-134 to Atar-142.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Ser-25 to Ala-30,<br>Gln-36 to Thr-48,<br>Arg-53 to Asn-67,<br>Glu-82 to Phe-93,<br>Ser-134 to Asn-142. |             | Asp-9 to Gln-17.       | Asp-26 to Leu-36,      | Leu-42 to Phe-50. | Ser-19 to Ser-25,<br>Pro-27 to Gly-33,<br>Pro-40 to Asn-47,<br>Pro-65 to Gln-70. | Pro-32 to Ser-39.                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 498                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 701                                                                                                     | 702         | 499                    | 500                    | 103               | 100                                                                              | 502                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 104 - 604                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 150 - 650                                                                                               | 1260 - 1340 | 88 - 324               | 311 - 373              | 300 37            | 65 - 585                                                                         | 192 - 530                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 104                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 307                                                                                                     | 308         | 105                    | 309                    | 107               | /01                                                                              | 108                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1003028                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 883427                                                                                                  | 847543      | 638231                 | 562772                 | 103707            | 634521                                                                           | 411332                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | нняска                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HHBCS39                                                                                                 | HHBCS39     | HHEAA08                | HHEAA08                | THIEFEAD          | HHFFJ48                                                                          | ннғнл59                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 94                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                         |             | 95                     | 96                     |                   | /6                                                                               | 86                                                                                 |

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| 3, 140(74.3, 1,0740.3, 3,0360.2, 5,9378.2, 10782.3, 3,0360.2, 5,9378.2, 10782.3, 2,0078.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10782.2, 10 | H0333: 1, H0597: 1 and<br>H0670: 1. | H0333: 1  | L0803: 6, H0052: 4, H0036: 17 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Lys-39 to Glu-45.                   |           |                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 503                                 | 504       | 505                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 140 - 289                           | 230 - 361 | 270 - 536                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 109                                 | 110       | 111                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | \$20198                             | 340818    | 662329                        |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 66                                  | 001       | 101                           |

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| 1,0665.3, 140574.2, 2,08059.2, 1,0765.2, 1,0805.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0905.4, 1,0 |           | L (10.49.9, 80.143.4.8. L0637.<br>3, L0780.3, L10662. 2,<br>2, L0751.2, L0777.<br>2, L0751.2, L0777.<br>4, L0772.1, L10338.1,<br>80049.1, H01024.1, H0135.<br>1, H0413.1, H0100.1,<br>H0647.1, L10772.1, L10659.<br>1, L0809.1 and L0759.1, L10659. | L0766; 7, L0731; 7, H0457;<br>6, H0051; 6, L0754;<br>L0803; 4, L0666; 4, H0140;<br>3, S0474; 3, H0052; 3,<br>L0157; 3, L0662; 3, L0659;<br>3, L562; 3, L0758; 3,<br>H0657; 2, S0140; 2, S0010; |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |           | Ser-16 to Val-33.                                                                                                                                                                                                                                   | Met-98 to Gin-107,<br>Giy-120 to Giy-126,<br>Pro-138 to Trp-145,<br>Leu-159 to Giy-169,<br>Val-211 to Arg-217,<br>Cys-256 to His-262,<br>Giu-320 to Val-327,                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 704       | 909                                                                                                                                                                                                                                                 | 507                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 270 - 302 | 62 - 217                                                                                                                                                                                                                                            | 183 - 1709                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 310       | 112                                                                                                                                                                                                                                                 | 113                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 383547    | 544615                                                                                                                                                                                                                                              | 695134                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HHGCM76   | ннбсодя                                                                                                                                                                                                                                             | HHPEN62                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |           | 102                                                                                                                                                                                                                                                 | 103                                                                                                                                                                                            |

| 1, 10628 2, 80066 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2, 10008 2,  | H0624: 1, S0360: 1, H0586:<br>, L0021: 1, T0041: 1 and<br>0779: 1. | S0442: 4, L0764: 4, S0408:<br>, H0306: 2, H0263: 2,<br>10596: 2, L0800: 2, L0755: |
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| Pite-399 to Asta-406, Asp. 444 to Ser-450, Pitol | Ala-28 to His-41, H06 Pro-43 to Gln-64. 1, L0 L077                 | Val-54 to Asp-59. S04<br>3, HG<br>H059                                            |
| <u>इ</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 508 Al                                                             | 509 Va                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 74 - 307                                                           | 66 - 392                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 114                                                                | 115                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 456466                                                             | 1307789                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HJABB94                                                            | HJACG02                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 104                                                                | 105                                                                               |

|                                                                       |                  |                                                                                   | _        | _                |                 | _                    | _                           | _                     | _                          | _                     | _                          | _                     | _                          |                       | _                          | _                     | _                         | _                     | _                          | _                     | _                          |                       | _                          | _                   | _                         | _                   | _                         | _                     | _                          | _                     | _                          | _                     | _                          |
|-----------------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------|----------|------------------|-----------------|----------------------|-----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|---------------------|---------------------------|---------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|
|                                                                       |                  |                                                                                   |          |                  |                 |                      |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       |                  |                                                                                   | -        |                  |                 |                      |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       |                  |                                                                                   |          |                  |                 |                      |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
| <u></u>                                                               |                  | 36: 15,X                                                                          |          |                  |                 |                      | :99                         |                       | áń                         |                       |                            |                       | <u></u>                    |                       | .i                         |                       |                           |                       | .9                         |                       |                            |                       | ÷:                         |                     | <u></u>                   |                     |                           |                       | ÷                          |                       |                            |                       |                            |
| 2, S0116: 1, S0358: 1,<br>H0489: 1, H0597: 1, T0041:<br>and L0772: 1. |                  | H0069: 3, T0041: 2, H0436: 15,X<br>, H0318: 1, L4747: 1,<br>0646: 1, L0766: 1 and |          |                  |                 | 17: 13,              | 10253: 11, H0457: 6, L0766: | 55: 4,                | 10559: 4, H0181: 4, L0748: | 51: 3,                | 10622: 3, L0770: 3, L0653: | 9:3,                  | 10341: 2, H0484: 2, S0049: | 24: 2,                | 10135: 2, H0040: 2, H0059: | 12: 2,                | 0002: 2, L0758: 2, L0588: | 4: 1,                 | 10650: 1, H0657: 1, H0656: | 4: 1,                 | H0637: 1, S6026: 1, S0300: | 19: 1,                | 10550: 1, S6014: 1, H0333: | 2: 1,               | 0427: 1, L0021: 1, H0599; | 50: 1,              | 0157: 1, S0050: 1, H0355: | 33: 1,                | 10068: 1, S0036: 1, H0038: | 72: 1,                | 10623: 1, T0041: 1, L4747: | 5: 1,                 | JU/61: 1, L0645: 1, L0648: |
| 2, S0116: 1, S0358: 1<br>H0489: 1, H0597: 1, 7<br>I and L0772: 1.     |                  | H0069: 3, T0041: 2, H<br>2, H0318: 1, L4747: 1,<br>20646: 1, L0766: 1 and         |          |                  |                 | H0618: 16, H0617: 13 | 11, H045                    | , L0769: 5, H0255: 4, | t, H0181                   | , H0170: 3, S0051: 3, | 3, L0770:                  | , L0743: 3, L0779: 3, | 2, H0484                   | , H0620: 2, H0424: 2, | 2, H0040                   | ; H0100: 2, T0042: 2, | ; L0758:                  | , H0171: 1, S0134: 1, | l, H0657                   | , S0116: 1, L0534: 1, | l, S6026:                  | , L0717: 1, H0549: 1, | 1, S6014:                  | L2504: 1, L2522: 1, | l, L0021:                 | H0545: 1, H0150: 1, | . S0050:                  | , H0252: 1, L0483: 1, | 1, S0036:                  | , H0087: 1, H0272: 1, | l, T0041:                  | , L3904: 1, L3905: 1, | , L0645                    |
| 2, S0116: 1, S0<br>H0489: 1, H059<br>1 and L0772: 1                   |                  | H0069:<br>2, H0318<br>L0646: 1                                                    | L0803: 1 |                  |                 | H0618:               | H0253:                      | 6, L0769              | H0559:                     | 4, H0170              | H0622:                     | 3, L0743              | H0341:                     | 2, H0620              | H0135;                     | 2, H0100              | S0002: 2                  | 2, H0171              | H0650: 1                   | 1, S0116              | H0637:                     | 1, L0717              | H0550: 1                   | 1, L2504            | H0427: 1                  | 1, H054             | L0157: 1                  | 1, H0252              | H0068: 1                   | 1, H008               | H0623: 1                   | 1, L3904              | <br>19/01                  |
|                                                                       |                  |                                                                                   |          |                  |                 |                      |                             | 'n                    | ٠,                         | 7,                    | 5,                         | _;                    |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | Asp-59.          | Asn-39.                                                                           |          | Pro-64.          | 3ly-8.          | His-41,              | Ala-67,                     | o Leu-15              | o Ser-16.                  | o Val-19              | to Pro-21                  | o Pro-252             |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | Val-54 to Asp-59 | Thr-26 to Asn-39.                                                                 |          | Pro-57 to Pro-64 | Lys-1 to Gly-8. | Glu-35 to His-41,    | Ser-62 to Ala-67,           | Pro-145 to Leu-155,   | Glu-157 to Ser-163,        | Arg-190 to Val-197,   | Asp-208 to Pro-215,        | Ser-247 to Pro-252.   |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | 705              | 510                                                                               |          |                  | 707             | 511                  |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | 373              | 425                                                                               |          | 439              | 715             | 1215                 |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | 47 - 373         | 291 - 425                                                                         |          | 50 - 439         | 350 - 715       | 232 - 1215           |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | 311              | 116                                                                               |          | 312              | 313             | 117                  |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | 509948           | 895505                                                                            |          | 821341           | 774300          | 719729               |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       | HJACG02          | HJACG30                                                                           |          | HJACG30          | HJACG30         | HJBCY35              |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       |                            |
|                                                                       |                  | 901                                                                               |          |                  |                 | 107                  |                             |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                     |                           |                     |                           |                       |                            |                       |                            |                       | 1                          |

| 1, L0662; 1, L0768; 1, L0768; 1, L0768; 1, L0659; 1, L0659; 1, L0659; 1, L0659; 1, L0659; 1, L2269; 1, L2269; 1, L2269; 1, L2269; 1, L2269; 1, L2269; 1, L0679; 1, L0679; 1, L0749; 1, L0749; 1, L0779; 1, L07 | 110556, L10771, 4, H0757, 4, H0763, 3, L0764, 3, L0764, 3, L0764, 3, L0764, 3, L0764, 3, L0762, 2, L0792, 2, L0482, 2, L0793, 2, L0792, 2, L0482, 2, L0794, 2, L0797, 2, L0492, 1, L0077, 2, L0376, 1, L0077, 1, L0777, 1, L0778, | H0494: 1                                                        |                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 512                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 513                                                             | 708                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 60 - 335                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 77 - 808                                                        | 008 - 69                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 811                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 611                                                             | 314                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 651337                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 862030                                                          | 665424                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HPAD75                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HKABZ65                                                         | HKABZ65                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 108                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 601                                                             |                                                                 |

| 3, 50194;<br>1, 1075;<br>1, 1075;<br>1, 1075;<br>1, 1075;<br>1, 1, 1075;<br>1, 1075;<br>1, 1075;<br>1, 1075;<br>1, 1075;<br>1, 1075;                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                      | 2, S0442:<br>: 1,<br>!, T0082:<br>4: 1,<br>., L0800:<br>:: 1,<br>, L0659:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| 8300-17. 89436-3, 80194;<br>8011-62, 18048-3, 80194;<br>10018-2, 18048-2, 10575;<br>10087-1, 18059-1, 12084-1,<br>10087-1, 18059-1, 12084-1,<br>10087-1, 18059-1, 12084-1,<br>10087-1, 18059-1, 18059-1,<br>18077-1, 1805-6, 1,<br>18077-1, 1805-6, 1,<br>18077-1, 1805-6, 1,<br>18077-1, 1805-6, 1,<br>18077-1, 1805-6, 1,<br>18077-1, 1805-1, 1805-1,<br>18097-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1, 1805-1, 1805-1,<br>1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 1805-1, 180                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                      | L0438: 2, L0758: 2, S0442: 1, S0354: 1, S0444: 1, 10741: 1, L0021: 1, T0082: 0, 44046: 1, H0494: 1, H0494: 1, L3815: 1, L5774: 1, L0802: 1, L5774: 1, L0803: 1, L0776: 1, L0659: 1, L0776: |
| S0366<br>S, 800<br>S, 400<br>S, 400<br>S, 100<br>S, 100 |                                                                                      | L0438<br>1, S03-5<br>H0741<br>1, H00<br>S0440:<br>1, L064<br>L0803:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 5-53,<br>to 1-86,<br>the 1-18,<br>the 1-13,<br>the 2-210,<br>the 2-210,<br>the 2-20,<br>the 2-20,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 5-53,<br>u-86,<br>fet-112,<br>fty-131.                                               | -13,<br>n-80,<br>yr-117,<br>ro-138,<br>he-153,<br>cr-325,<br>lis-372,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Named to the 53, Named to the 64, Named                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Thr-42 to Pro-53,<br>Val-78 to Glu-86,<br>Glu-103 to Mct-112,<br>Ala-124 to Gly-131. | Thr-6 to Trp-13,<br>Thr-75 to Gin-80,<br>Thr-112 to Tyr-117,<br>Leu-133 to Pro-138,<br>Ala-146 to Phe-153,<br>Gin-319 to Ser-325,<br>Val-354 to His-372,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 418                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 709                                                                                  | 515                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 38 - 940                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 35 - 499                                                                             | 501 - 1814                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 120                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 315                                                                                  | 121                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 1352202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 552465                                                                               | 1352263                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| HKACDS8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HKACD58                                                                              | HKAEV06                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                      | ==                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| 1, L2655: 1, L2653: 1,<br>S0374: 1, H0547: 1, H0672: | , S0330: 1, H0521: 1,<br>10696: 1, L0439: 1, L0752: | , L0594: 1 and H0543: 1. |                  | S0474: 5, S0422: 3, H0580: | 2, S0444: 1, H0494: 1 and<br>H0543: 1. |                   |                   | L0747: 4, L0766: 3, L0776: | , L0665: 3, H0328: 2, | .0763: 2, L0769: 2, L0772: | ; L0764: 2, L0666: 2, | .0745: 2, L0750: 2, L0777: | , L0759: 2, L0608: 2, | 10556: 1, S0116: 1, H0384: | , S0360: 1, S0408: 1, | H0637: 1, H0722: 1, H0735: | , H0619: 1, H0492: 1, | I0156: 1, H0421: 1, H0620: | , S0051: 1, H0083: 1, | 10510: 1, H0266: 1, H0031: | , H0634: 1, H0560: 1, | 0440: 1, H0132: 1, H0695: | , L0800: 1, L0521: 1, | .0662: 1, L0774: 1, L0806: | , L0807: 1, H0144: 1, | I0690: 1, H0658: 1, H0521: | , H0522: 1, L0439: 1, | .0746: 1, L0752: 1, L0480: | , L0589: 1, L0592: 1, | 10543: 1 and H0422: 1. |                 |                   | L0794: 11, H0521: 11, | S0002: 8, L0805: 8, L0803: |
|------------------------------------------------------|-----------------------------------------------------|--------------------------|------------------|----------------------------|----------------------------------------|-------------------|-------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|------------------------|-----------------|-------------------|-----------------------|----------------------------|
| Pro-391 to Gly-396, I                                |                                                     |                          | Thr-6 to Trp-13. | Ser-51 to Thr-57.          |                                        | Ser-51 to Thr-57. | Gln-23 to Asp-28. | Ser-7 to Pro-14,           | 1.1                   |                            | CI                    | Leu-162 to Ala-167, I      | Gly-172 to Asn-177, 2 | Thr-226 to Ala-232.        |                       |                            |                       |                            | _                     | =                          |                       | v <sub>1</sub>            | -                     | 2                          | _                     | <u> </u>                   |                       | _                          | 1                     |                        | Met-1 to Tyr-6, | Thr-38 to Ala-44. |                       | 9,                         |
|                                                      |                                                     |                          | 710              | 516                        |                                        | 711               | 712               | 517                        |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                       |                        | 713             |                   | 518                   |                            |
|                                                      |                                                     |                          | 197 - 370        | 508 - 831                  |                                        | 508 - 831         | 234 - 347         | 178 - 879                  |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                       |                        | 30 - 170        |                   | 64 - 1473             |                            |
|                                                      |                                                     |                          | 316              | 122                        |                                        | 317               | 318               | 123                        |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                       |                        | 319             |                   | 124                   |                            |
|                                                      |                                                     |                          | 638238           | 946512                     |                                        | 889258            | 904190            | 876571                     |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                       |                        | 654871          |                   | 1352286               |                            |
|                                                      |                                                     |                          | HKAEV06          | HKAFT66                    |                                        | HKAFT66           | HKAFT66           | HKB1E57                    |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                       |                        | HKB1E57         |                   | HKFBC53               |                            |
|                                                      |                                                     |                          |                  | 112                        |                                        |                   |                   | 113                        |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                       |                            |                       |                        |                 |                   | 114                   |                            |

| 8.8 8078; 6.8 8144; 6.10774; 11.0774; 83029; 5.8 8144; 6.10774; 11.0774; 83029; 5.8 8144; 6.10774; 11.076; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; 1.2 8029; |                                                                                                |                                      |                                      | 104942-18, L09803-25, L00803-25, L00803-2, L0074; L0774; L0774; L0774; L0774; L0774; L0774; L0776-2, L |
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| Gly-15to Gly-15to Gly-16t, 7, 80 (Gly-16t) Gly-46t, 17, 81 (Gly-46t) Gly-46t, 17, 81 (Gly-46t) Gly-46t, 17, 81 (Gly-46t) Gly-46t, 17, 18 (Gly-46t) Gly-46t, 18 (Gly-46t) Gly-46t | Ala-28 to Ala-33, Arg-38 to Leu-48, Thr-120 to Lys-125, Gly-155 to Gln-163, Gly-200 to Gln-214 | Ala-1 to Gly-6,<br>Ala-10 to Tvr-18. | Ala-1 to Gly-6,<br>Ala-10 to Tvr-18. | 99,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|-----------|-----------|------------------------------------------------------------------------------|------------------------------------------------------|----------------------------|------------------------------------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|-------------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|-------------------------------|
|           |           |                                                                              |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           |           | .0769:                                                                       | .0748:                                               | 0358:                      | 0787                                                 |                        | I0309:                     |                        | .0768:                     |                        | 0027: 2,                      | .0756:                     | _                      | 10624:                     |                        | 10717:                     |                        | 30418:                     | _                      | T0393:                     |                        | r0040:                     | _                     | I0530:                     |                       | H0123:                     |                        | 10622:                     |                        | H0135:                     |                        | 30144:                     | ,L0520:                       |
| H0506: 1. | H0431:1   | L0758: 10, L0731: 8,<br>L0747: 7, H0545: 6, L0769:<br>6, L0809: 6, L0740: 6, | L0803: 5, L0775: 5, L0748:<br>5, L0755: 5, S0360: 4, | L0749: 4, L0757: 4, S0358: | 5, H0722: 3, L0771: 3,<br>1 0774: 3 1 0657: 3 1 0782 | 3, L0789; 3, T0049; 2, | H0638: 2, S0278: 2, H0309: | 2, H0266: 2, S0438: 2, | H0652: 2, L0770: 2, L0768: | 2, L0794: 2, L0518: 2, | L0666: 2, S0126: 2, S0027: 2, | L0743: 2, L0751: 2, L0756: | 2, L0753: 2, L0759: 2, | L0593: 2, S0192: 2, H0624: | 1, H0171: 1, H0556: 1, | L3644: 1, S0040: 1, H0717: | 1, H0295: 1, H0484: 1, | H0661: 1, H0305: 1, S0418: | 1, S0442: 1, S0408: 1, | H0730: 1, H0747: 1, H0393: | 1, H0441: 1, H0333: 1, | H0574: 1, H0486: 1, T0040: | 1, L3657: 1, S0280: 1 | H0746: 1, L0738: 1, H0530: | 1, H0544: 1, H0046: 1 | H0041: 1, H0571: 1, H0123: | 1, H0024: 1, H0510: 1, | S0314: 1, S0003: 1, H0622: | 1, T0006: 1, H0644: 1, | H0617: 1, H0673: 1, H0135: | 1, H0163: 1, H0634: 1, | H0616: 1, H0551: 1, S0144: | 1, S0142: 1, S0422: 1, L0520: |
|           |           | Arg-35 to Ala-41,<br>Phe-55 to Arg-61,<br>Lys-152 to His-163.                |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           | 521       | 522                                                                          |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           | 202 - 327 | 238 - 726                                                                    |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           | 127       | 128                                                                          |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           | 581399    | 1352197                                                                      |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           | HKMMW74   | HLDNA86                                                                      |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |
|           | 117       | 118                                                                          |                                                      |                            |                                                      |                        |                            |                        |                            |                        |                               |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                       |                            |                       |                            |                        |                            |                        |                            |                        |                            |                               |

| L556:-1, L3905:-1, L0373:<br>1, L064:-1, L068:-1,<br>1, L080:-1, L083:-1,<br>1, L080:-1, L065:-1,<br>1, L060:-1, L065:-1, L562:-1,<br>1, L060:-1, L662:-1, L662:-1,<br>1, L060:-1, L662:-1, L662:-1,<br>1, L060:-1, L662:-1, L662:-1,<br>1, L070:-1, S004:-1, L915:-1,<br>1, L070:-1, S004:-1, L915:-1,<br>1, L070:-1, S004:-1, L915:-1,<br>1, L070:-1, S004:-1, L916:-1,<br>1, L070:-1, S004:-1,<br>1, L070:-1, S004:-1,<br>1, L070:-1, S004:-1,<br>1, L070:-1, S004:-1,<br>1, L0 |                   | 1,000; 8, 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; 1,009; |
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| 88007; 14.071;<br>1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10438; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.10431; 1.1043 | LU786, 6, H0012.<br>LU786, 6, H0012.<br>LU7876, 6, H0012.<br>LU7875, 1, H0059.<br>LU7875, 1, H0059.<br>LU7875, 1, H0048.<br>LU7875, 1, H0049.<br>LU7875, 1, H0049.<br>LU7875, 1, L08875, 1, L08875.<br>LU686. 2, L08875.<br>LU686. 2, H00877.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Arg-122 to Sec-139, S900, Met-144 to Gla-149, 15,000, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009, 10,009,     | Loctues to Lyst 74, 1.074  Check St. 1975-109 to Lyst 15, 1.076  Lyst 2070 to Lyst 214, 4, 1100  Lyst 2070 to Lyst 214, 4, 1100  Ana 271 to Thr. 279, 1.075  Chin 242 to Chyst 34, 1100  Chin 242 to Chyst 34, 1100  Lock 21, 100  Lock 21, 100 |
| 224                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 525 LL C C C C C C C C C C C C C C C C C C                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 520 - 1005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 99 - 1142                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 130                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 131                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| K62 755742                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 740755                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 120 HLDQR62                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 нг. Бор. 79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| 80126-2, 10670-2, 10740: 2, L0754-2, L0750-2, 1, 10751-1, 140621, 1, 10751-1, 140621, 1, 10751-1, 140621, 1, 10751-1, 14073-1, 1338-1, 1, 10751-1, 14073-1, 1338-1, 1, 10751-1, 14073-1, 1338-1, 1, 10751-1, 14073-1, 14073-1, 1, 10751-1, 14073-1, 14073-1, 1, 10751-1, 14073-1, 14073-1, 1, 10751-1, 14073-1, 14073-1, 1, 10751-1, 14073-1, 14073-1, 1, 10772-1, 10773-1, 10773-1, 1, 10772-1, 10773-1, 10773-1, 1, 10772-1, 10773-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1073-1, 1, 10772-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1, 1073-1 | H0024: 1          | L0157; 7, L0794; 6, H0040;<br>1, L0439; 4, L0758; 4,<br>1, L0471; 2, H0055; 3, L0005;<br>1, L0471; 2, H0059; 2, L0761;<br>1, L0804; 2, L0769; 2, L0761;<br>1, L0805; 2, T0002; 1,<br>1, L0805; 2, T0001; 1,<br>10685; 1, 50134; 1, 50110; |
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| 0.0.1-1-1-1-1-1-1-1-0-1-0-1-0-1-0-1-0-1-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Leu-32 to His-38. | 4 # 0   0 #                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Г                 | 527 N                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 30 - 164          | 186 - 338                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 132               | 133                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 684216            | 778073                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLHAL68           | HLIBD68                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 122               | 123                                                                                                                                                                                                                                       |

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| (1,10176, 1,80356, 1,<br>90222, 1,10441; 1,10446<br>1,10466, 1,10014; 1,00083; 1,10036, 1,10038; 1,10038; 1,10038; 1,10038; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10039; 1,10049; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1,100799; 1, | 1, 10078; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10778; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 10779; 1, 107 | H0722: 2, H0574: 2, H0742:<br>and H0730: 1.                                          |         | H0036: 2, S0132: 1, S0010:<br>, S0250: 1, H0591: 1 and<br>H0130: 1. | H0170: 1, S6026: 1 and 10591: 1.                                               |                 |
| 1, HG<br>S022<br>1, HG<br>H008<br>H008<br>1, L0<br>L038<br>1, HG<br>L038<br>1, HG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | - 10 8 1 H 1 H 1 H 1 H 1 H 1 H 1 H 1 H 1 H 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                      |         | H00<br>1, S0<br>H013                                                |                                                                                |                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Pre-55 to Cily-66, Phe-92 to Leu-103                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Arg-54 to Asn-65,<br>Glu-80 to Ala-87,<br>Val-170 to Arg-175,<br>Arg-185 to Arg-190. |         |                                                                     | Gly-4 to Glu-9,<br>Asp-22 to Cys-28,<br>Glu-39 to Lcu-44,<br>Phe-88 to Phe-94. | Gly-4 to Glu-9. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 528                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 529                                                                                  | 719     | 530                                                                 | 531                                                                            | 720             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 249 - 869                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 10 - 582                                                                             | 3 - 575 | 5 - 232                                                             | 226 - 516                                                                      | 226 - 423       |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | нг.гсүм                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HLQDR48                                                                              | HLQDR48 | HLTHR66                                                             | HLTIP94                                                                        | HLTIP94         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 124                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 125                                                                                  |         | 126                                                                 | 127                                                                            |                 |

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|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
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| 1047690                                                                                                                      | 629552                                                    |
| HLTIP94                                                                                                                      | нгмлліт                                                   |
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| (1992) 1. (1982) 1. (1993) 1. (1992) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) 1. (1993) | L0439: 16, L0748: 12,<br>L0758: 9, H0013: 6, L0740:<br>5, L0754: 5, S0474: 4,<br>H0265: 3, H0556: 3, H0619: |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLWBK05                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 129                                                                                                         |

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| 3, 80                 | 3.00 | 8035                      | 7, 30<br>H062              | 2, H0                 | H010                      | 2, LO               | L037                      | 2, LO                 | L051                      | 2, 10                 | F028                      | 2. HO               | H066                       | 95              | 8047                         | 1.002                 | 1. HO               | H005                       | 1, H0               | H027                      | 1, H0               | H067                      | 1, H0                 | L035                      | 1, SO               | L076                      | 01,10               | L077                      | 1, LO               | F066                      | 1, H0               | H065                      | 1, H0                 | 690H                       | 1, S0                 | L074                       |
|                       |      |                           |                            |                       |                           |                     |                           |                       |                           |                       |                           |                     |                            |                 |                              |                       |                     |                            |                     |                           |                     |                           |                       |                           |                     |                           |                     |                           |                     |                           |                     |                           |                       |                            |                       |                            |
|                       |      |                           |                            |                       |                           |                     |                           |                       |                           |                       |                           |                     |                            |                 |                              |                       |                     |                            |                     |                           |                     |                           |                       |                           |                     |                           |                     |                           |                     |                           |                     |                           |                       |                            |                       |                            |
|                       |      |                           |                            |                       |                           |                     |                           |                       |                           |                       |                           |                     |                            |                 |                              |                       |                     |                            |                     |                           |                     |                           |                       |                           |                     |                           |                     |                           |                     |                           |                     |                           |                       |                            |                       |                            |

| , S0026: 1, S0196: 1, S0412:<br>and H0506: 1. | Interess. 7, 140-77; 1, 100-77; 1, 100-77; 1, 100-77; 4, 100-77; 4, 100-77; 4, 100-77; 4, 100-77; 4, 100-77; 4, 100-77; 4, 100-75; 2, 100-91; 1, 100-75; 2, 100-91; 1, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2, 100-75; 2 | LI (LOHS) 9, 100-87, 100-100-100-100-100-100-100-100-100-100 |
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| ===                                           | <u>- 45 65 43 3 - 3 - 8 - 3 - 5</u> - 5 - 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <u> </u>                                                     |
|                                               | 534                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 535                                                          |
|                                               | 432 - 1130                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 155 - 328                                                    |
|                                               | 140                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 141                                                          |
|                                               | 797609                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 460619                                                       |
|                                               | н.<br>Н. М. В. У. Б.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HLWCF05                                                      |
|                                               | 130                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 131                                                          |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 536      | 537                                                  | 722       | 538                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 92 - 232 | 383 - 613                                            | 254 - 418 | 280 - 531                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 142      | 143                                                  | 328       | 144                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 778075   | 1352203                                              | 553507    | 553514                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLYAC95  | HLYAN59                                              | HLYAN59   | HLYAP91                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 132      | 133                                                  |           | 134                        |

| , H0039: 1, H0622: 1,<br>10634: 1, L0769: 1, L0800:<br>, L0764: 1, L0648: 1,<br>20794: 1, L0789: 1, H0696:<br>, L075: 1, L077: 1,<br>0756: 1, L0731: 1 and<br>10445: 1, | H0687: 2 and H0445: 1. | 1, 1078.2, 10.43.9, 10.776.<br>1, 1079.2, 10.43.9, 10.776.<br>1, 1078.4, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78.1, 10.78. | 20056. 1, LO701. 1, LO040. |
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|                                                                                                                                                                         |                        | Gly-43 to Gly-55.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                            |
|                                                                                                                                                                         | 539                    | 540                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                            |
|                                                                                                                                                                         | 69 - 287               | 191-613                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                            |
|                                                                                                                                                                         | 145                    | 146                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                            |
|                                                                                                                                                                         | 638042                 | 561941                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                            |
|                                                                                                                                                                         | HLYES38                | HMADK33                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                            |
|                                                                                                                                                                         | 135                    | 136                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                            |

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| 005:<br>006:<br>521:<br>500:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 5575:<br>118:<br>083:<br>133:<br>42: 1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 442:<br>0222:<br>769:<br>106:                                                                                                                                                                                           |                                                             | 3497:                      |
| 1, 1,065; 1,1,075; 1, 1,1,078; 1, 1,0768; 1, 1,078; 1, 1,0708; 1, 1,0078; 1, 1,0078; 1, 1,0078; 1, 1,0078; 1, 1,0089; 1, 1,0088; 1, 1,0088; 1, 1,0098; 1, 1,0098; 1, 1,0098; 1, 1,0098; 1, 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0098; 1,0099; 1,0098; 1,0098; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0099; 1,0 | LOD94-LOT55.3, H0575.<br>LOSO0-LOSO0-LOT99-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-LOSO0-L | H0624: 2, S0354: 2, S0442: ., S0444: 1, S0272: 1, S0444: 1, S0272: 1, H0886: 1, L0021: 1, L0036: 1, H0031: 1, L0749: 1, L0687: 1, H0521: 1, S0406: 1, H0521: 1, S0406: 1, L0748: 1 and S0462: 1, L0748: 1 and S0462: 1. |                                                             | L0800: 2, H0550: 1, H0497: |
| <u> </u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Gly-33 to Lys-41,  Gly-32 to Lys-60,  Asn-81 to Ala-86,  Lys-156 to Met-164,  Gln-283 to Lys-292,  Glu-303 to Gly-308.                                                                                                  | Gly-33 to Lys-41,<br>Pro-52 to Lys-60,<br>Asn-81 to Ala-86. |                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 541                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 542 Gly Pro- Asn Lys Glu Glu                                                                                                                                                                                            | 723 Gly<br>Pro-<br>Asn                                      | 543                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 267 - 533                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 4 - 1023                                                                                                                                                                                                                | 3 - 923                                                     | 175 - 369                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 147                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 148                                                                                                                                                                                                                     | 329                                                         | 149                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 596831                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1352406                                                                                                                                                                                                                 | 1049263                                                     | 105559                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HMADS41                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HMAMI15                                                                                                                                                                                                                 | HMAMIIS                                                     | HMCFY13                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 137                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 138                                                                                                                                                                                                                     |                                                             | 139                        |

| , S0344: 1, L0769: 1,<br>.0789: 1 and L0749: 1. | L0809; 2, H0346; 1, H0271;<br>, L0774; 1 and L0532; 1. | L0439; 20, L0157; 8, 0794; 8, L0805; 6, H0739; 10731; 5, L0804; 4, 0731; 5, L0804; 4, 0737; 3, L0764; 3, L0764; 4, 0737; 4, 0737; 5, L0764; 5, L07 | , 80356: 2, H0741: 2,<br>10050: 2, S0144: 2, L0803: | , LU655: 2, LU665: 2,<br>2654: 2, H0521: 2, H0522:<br>1.0749-2-1.0779-2 | , 70777: 2, L0755: 2, L0759:<br>. H0265: 1, S6024: 1, | 0116: 1, S0444: 1, H0733:<br>S6026: 1 H0208: 1 | 10592: 1, L0622: 1, H0486: | , H0013: 1, H0250: 1,<br>10635: 1, H0156: 1, S0474: | , H0581: 1, H0046: 1,<br>0471: 1 H0012: 1 H0014: | H0373: 1, H0073: 1, | 10266: 1, S0336: 1, H0039:<br>S0036: 1, H0040: 1, | 10634: 1, H0551: 1, H0561: | , S0438: 1, S0440: 1,<br>0529: 1, L0769: 1, L0764: | L0662: 1, L0774: 1, | 00775: 1, L0809: 1, L0790: | 207.72. 1, E0000. 1,<br>0664: 1, E0665: 1, E0709: | L2653: 1, H0144: 1, | .0659: 1, H0658: 1, H0670: | , 503/8: 1, H0596: 1,<br>10555: 1 H0576: 1 S0038: | , L0745: 1, L0747: 1, | .0780: 1, S0434: 1, S0436: 1 | 00:1.         |
|-------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------|------------------------------------------------|----------------------------|-----------------------------------------------------|--------------------------------------------------|---------------------|---------------------------------------------------|----------------------------|----------------------------------------------------|---------------------|----------------------------|---------------------------------------------------|---------------------|----------------------------|---------------------------------------------------|-----------------------|------------------------------|---------------|
| 1, S0344<br>L0789: 1                            | L0809:                                                 | 7.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <u>0 € ± 6</u>                                      | L2654: 2<br>1.0740                                                      | L0777:                                                | S0116: 1                                       | H0592:                     | I, H001<br>H0635:                                   | 1, H058                                          | 1, H037.            | H0266:                                            | H0634:                     | 1, S0438<br>H0529;                                 | 1, L0662            | L0775: 1                   | L0664: 1                                          | 1, L2653            | H0659:                     | 1,505/2                                           | 1, L074               | L0780:                       | and mooos: 1. |
|                                                 |                                                        | Gln-85 to Lys-91,<br>Pro-106 to Ser-117,<br>Pro-124 to Ala-130,<br>Tra-154 to Tra-160                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | or-dir or-ci-dir                                    |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              |               |
|                                                 | 544                                                    | 545                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                     |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              |               |
|                                                 | 273 - 407                                              | 34 - 699                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                     |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              |               |
|                                                 | 150                                                    | 151                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                     |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              |               |
|                                                 | 929099                                                 | 560775                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                     |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              |               |
|                                                 | HMDAB56                                                | HMEED18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                     |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              | 1             |
|                                                 | 140                                                    | 141                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                     |                                                                         |                                                       |                                                |                            |                                                     |                                                  |                     |                                                   |                            |                                                    |                     |                            |                                                   |                     |                            |                                                   |                       |                              |               |

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|                                                                                                                                                                           |                                  |                                                                                                            |                                                             |           |         |           |                                                                                                                                                                                                                 |                                                                                                                                                                                                        |
|                                                                                                                                                                           |                                  | 3,3p                                                                                                       |                                                             |           |         |           |                                                                                                                                                                                                                 |                                                                                                                                                                                                        |
| L0757:3, L0662:2, H0686:<br>7, 8044:1, H0766:1,<br>0055:1, L0763:1, L0800:<br>1, L0764:1, L0768:1,<br>0805:1, L0768:1,<br>1, H0699:1, H0672:1,<br>1, H0699:1, L0777:1 and | H0266: 1, L0438: 1 and 20439: 1. | L0517: 2, S0050: 1, H0014: 3,3p<br>1, H0510: 1, H0040: 1,<br>H0264: 1, S0002: 1, S0374: 1<br>and L0758: 1. |                                                             |           |         | S0002: 1  | L0560: 5, L0545: 4, S0002.<br>L0574: J. E574: 2, H0240: 1,<br>80046: 1, H0333: 1, H0597:<br>L1 H0014: 1, L5569: 1,<br>L0533: 1, L0519: 1, L0544:<br>L5 8034: 1, H0520: 1,<br>80454: 1, S0406: 1 and<br>3813: 1, | LD794; S. L0766; 14,<br>10457; 10, L0809; 8, L0761;<br>7, L0659; 7, L0764; 6,<br>10, 10, 10, 10, 10, 10, 10, 10, 10, 10,                                                                               |
|                                                                                                                                                                           | Ser-34 to Ser-39.                | Ser-31 to Lys-45,<br>Pro-47 to Pro-53,<br>Ser-58 to Arg-63.                                                | Ser-31 to Lys-45,<br>Pro-47 to Pro-53,<br>Ser-58 to Arg-63. |           |         |           | Met-1 to Gly-7.                                                                                                                                                                                                 | Thr-23 to Lys-31,<br>Leu-1 for Giu-121,<br>Asp-15 to Thr-161,<br>Giy-164 to Arg-170,<br>Ser-216 to Giy-256,<br>Fre-239 to Giu-266,<br>Arg-240 to Giu-260,<br>Arg-241 to Giu-368,<br>Arg-341 to Giu-38, |
| 546                                                                                                                                                                       | 547                              | 548                                                                                                        | 724                                                         | 725       | 726     | 549       | 550                                                                                                                                                                                                             | 551                                                                                                                                                                                                    |
| 332 - 451                                                                                                                                                                 | 92 - 280                         | 531 - 725                                                                                                  | 528 - 722                                                   | 565 - 645 | 2 - 151 | 120 - 308 | 272 - 421                                                                                                                                                                                                       | 256 - 3129                                                                                                                                                                                             |
| 152                                                                                                                                                                       | 153                              | 154                                                                                                        | 330                                                         | 331       | 332     | 155       | 156                                                                                                                                                                                                             | 157                                                                                                                                                                                                    |
| 520307                                                                                                                                                                    | 520304                           | 973996                                                                                                     | 895429                                                      | 904241    | 750927  | 560229    | 427121                                                                                                                                                                                                          | 1301451                                                                                                                                                                                                |
| HMEFT54                                                                                                                                                                   | HMEGF92                          | HMSDL37                                                                                                    | HMSDL37                                                     | HMSDL37   | HMSDL37 | HMSF126   | HMSJU68                                                                                                                                                                                                         | HMTBI36                                                                                                                                                                                                |
| 142                                                                                                                                                                       | 143                              | 441                                                                                                        |                                                             |           |         | 145       | 146                                                                                                                                                                                                             | 147                                                                                                                                                                                                    |

| 2, 10703; 2, 10743; 2, 10703; 2, 10704; 2, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 10705; 1, 107 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Gln-387 to Plnc-398,<br>Lett-320 plnc-435,<br>Tyr-485 to Re-463,<br>Tyr-480 to Ala-496,<br>Thr-518 to Ala-235,<br>Lys-242 to Lett-549,<br>Prn-627 to Re-631,<br>Ser-821 to Alg-827,<br>Gln-921 to Ser-927,<br>Ala-929 to Re-941,<br>Ser-945 to Arg-937.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | The 25 to Lys 31,<br>Lear 116 to (the 121,<br>Asp. 155 to The 161,<br>(dly-fela Argel 701,<br>Sez-216 to (dly-226,<br>Pro-229 to (dla-226,<br>Arge-240 to (dla-226,<br>Arge-341 to (dla-236,<br>Lys-36 to Sez-364,<br>(los-376 to Sez-364,<br>(los-376 to Pro-439,<br>Try-489 to Pro-439,<br>Try-489 to Pro-435,<br>Try-489 to Re-435,<br>Try-489 to Argel 40,<br>Try-489 to Re-435,<br>Try-489 to Argel 40,<br>Try-489 to Argel 40,<br>Try-489 to Argel 40,<br>Try-480 to Argel |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 727                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                                                                                                       | HIOS4-4 L0775: 3.1 HO44-1. L0748: 1. HO54-4. L0775: 2. H004-6. 2. H004-6. 2. L0715: 2. L0771-2. L0771-                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | H0341: 2, L0303: 2, L0439: 2, L0747: 2, S0376: 1, S0360; 1, S0222: 1, H0674: 1, H0674: 1, H0638: 1, L0656: 1, L0899: 1, L0666: 1, L0754: 1, L0756: 1, L0757: 1 and |
| Pro-627 to Ile-632,<br>Ser-637 to Arg-651,<br>Ser-821 to Gly-827,<br>Gli-921 to Ser-927,<br>Arg-932 to Ile-941,<br>Ser-945 to Arg-957 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2 - 4 - 1                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                       | 552                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 553                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                       | 34 - 453                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 124 - 252                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                       | 158                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 159                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                       | 639203                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 460487                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                       | HMVBSSI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HMWDC28                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                       | 148                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 149                                                                                                                                                                                                                                                                                                            |

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| L         |          |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                     |                                                                                                        |                                                                      |                                        | Ц                 | 1         | 1                  |                                                                                                                                                                                                                     | =               | _               |
| L0591: 1. | H0341: 1 | L0747: 2, L0758: 2, H0580:<br>1 and H0179: 1. | H0521: 6, H0036: 2, H0052: 2, H0051: 2, H0521: 4, H0543: 2, H0543: 2, H0543: 2, H0543: 1, S0354: 1, H0392: 1, H0063: 1, H0063: 1, H0063: 1, H0652: 1, H0520: 1, H0541: 1, S036: 1, L0593: 1, H0500: 1, H0502: 1, H0502: 1, H0502: 1, H0502: 1, H0502: 1, H0500: 1, H0502: | H0556: 2, H0271: 2 and<br>H0619: 1. | L0539: 1, S0442: 1, H0619: 1, H0581: 1, T0010: 1, H0416: 1, H0622: 1, H0131: 1, H0521: 1 and H0653: 1. | H0271: 2, H0581: 1, H0051:<br>1, H0163: 1, L0599: 1 and<br>H0422: 1. | 80052: 1                               | S0052: 2          | S0052: 1  | \$0052:1           | L0749: 4, L0439: 3, H0100:<br>2, L0770: 2, L0776: 2,<br>H0556: 1, H0638: 1, H0441:<br>1, T0010: 1, H0687: 1,<br>L0055: 1, L0769: 1, L0809:<br>1, S0428: 1, H0522: 1,<br>H0694: 1, L0758: 1, L0889:<br>mad L0592: 1, | S0428; 1        |                 |
|           |          |                                               | Asp-21 to Ser-29.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Pro-97 to Asp-104.                  | Pro-47 to Met-53,<br>Ser-130 to Ser-138.                                                               | Val-25 to Gly-33.                                                    | Asp-15 to Tyr-21,<br>Pro-29 to Asn-39. | Asp-45 to Thr-50. | 0 0       | Pro-18 to Gits-25. | Asn-46 to Ser-54.                                                                                                                                                                                                   | Met-1 to Gly-9. | Met-1 to Gly-9. |
|           | 554      | 555                                           | 556                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 557                                 | 558                                                                                                    | 529                                                                  | 260                                    | 195               | 562       | 564                | 565                                                                                                                                                                                                                 | 999             | 728             |
|           | 72 - 437 | 213 - 428                                     | 488 - 691                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 206 - 637                           | 228 - 929                                                                                              | 86 - 286                                                             | 185 - 523                              | 72 - 320          | 108 - 380 | 77 - 217           | 388 - 636                                                                                                                                                                                                           | 27 - 200        | 27 - 200        |
|           | 160      | 191                                           | 162                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 163                                 | 164                                                                                                    | 165                                                                  | 991                                    | 167               | 891       | 170                | 171                                                                                                                                                                                                                 | 172             | 334             |
|           | 562063   | 553558                                        | 753337                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 768395                              | 634551                                                                                                 | 577013                                                               | 532619                                 | 920664            | 553552    | 561568             | 839224                                                                                                                                                                                                              | 1041375         | 838184          |
|           | HMWFT65  | HNEEE24                                       | HNFFC43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HNFGF20                             | HNFIY77                                                                                                | HNFJF07                                                              | HNGDJ72                                | HNGEP09           | HNGFR31   | HNGJES0            | HNGND37                                                                                                                                                                                                             | HNGOI12         | HNGOI12         |
|           | 150      | 151                                           | 152                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 153                                 | 154                                                                                                    | 155                                                                  | 156                                    | 157               | 158       | 651                | 191                                                                                                                                                                                                                 | 162             |                 |

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|           | S0053: 1 | L047: 5, 1069; 4, 5946;<br>L4039; 4, 1077; 4,<br>H067: 2, 1077; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; 2, 1079; | S0053: 2 and S0428: 1. | S0216: 1                               | S0216: 1 | 1100.2-3.1 (1974-4)<br>1407.0-3.3 (1974-4)<br>15388.2, 106.9-2, 100.7-1<br>15.94.6-2, 101.0-1<br>16.07.3-1, 100.5-1, 100.4-1<br>16.07.3-1, 100.2-1, 100.3-1<br>16.07.3-1, 100.4-1, 100.9-1<br>1, 100.3-1, 100.9-1, 100.9-1, 100.9-1<br>1, 100.3-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, 100.9-1, |
|           |          | Gla-67 to Ala-74.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                        | Glu-17 to Lys-30,<br>Val-43 to Asn-53. |          | Pro-Se to Pro-63,<br>Met-92 to The-98,<br>Sez-112 to Pro-120,<br>Pro-120, to Gila-173,<br>Ala-200 to Sez-210,<br>Lys-311 to Asn-320.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 729       | 292      | 888                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 569                    | 570                                    | 571      | 572                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 596 - 877 | 57 - 302 | 38 - 280                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 71 - 307               | 40 - 201                               | 12 - 251 | 28 - 990                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 335       | 173      | 174                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 175                    | 176                                    | 177      | 178                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 839283    | 634851   | 664507                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 646709                 | 895462                                 | 843488   | 1310821                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| HNGOI12   | HNHEU93  | HNHFM14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HNHFR04                | HNHNB29                                | HNHOD46  | HNTBI26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|           | 163      | 164                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 165                    | 166                                    | 167      | 891                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|        |                                                                                      |                                                               | L0794; 3, L0663; 2, S0360;<br>1, 1002; 1, L0353; 1,<br>1, 10150; 1, L0353; 1,<br>1, 10538; 1, L0804; 1,<br>1, 10538; 1, L0804; 1,<br>1, 10538; 1, L0777; 1,<br>1, 1077; 1, L0777; 1,<br>1, 1077; 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, | 10.0809.5, 1,0404.5, 10.081.6, 1,0406.5, 1,0406.5, 1,0406.4, 1,048.4, 1,048.4, 1,048.4, 1,048.4, 1,048.4, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048.2, 1,048 |
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| 977978 | Pro-56 to Pro-63,<br>Met-92 to Thr-98,<br>Ser-112 to Pro-120,<br>Pro-162 to Ser-169. | Pro-56 to Pro-63,<br>Met-92 to Thr-98,<br>Arg-107 to Pro-120. |                                                                                                                                                                                                                                         | Typ-2 to Galy-15, 117-7 to Galy-15, 117-7 to Galy-15, 117-17 to Galy-15, 117-17 to Galy-15, 117-17 to Galy-15, 117-17 to Galy-17 to  |
|        | 730                                                                                  | 731                                                           |                                                                                                                                                                                                                                         | 574                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|        | 32 - 547                                                                             | 16 - 411                                                      | 100 - 447                                                                                                                                                                                                                               | 111 - 1316                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|        | 336                                                                                  | 337                                                           | 179                                                                                                                                                                                                                                     | 180                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|        | 796807                                                                               | 590738                                                        | 545534                                                                                                                                                                                                                                  | 1160395                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|        | HNTB126                                                                              | HNTBI26                                                       | HNTBL27                                                                                                                                                                                                                                 | HNTCE26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|        |                                                                                      |                                                               | 169                                                                                                                                                                                                                                     | 170                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| (10092.1, 80344 1, 80002.<br>1, 10364.1, 10364.1, 10364.1, 10364.1, 10376.1, 10376.1, 10366.1, 10466.1, 10466.1, 10468.1, 10468.1, 10669.1, 10609.1, 10609.1, 10609.1, 10099.1, 10399.1, 10394.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10499.1, 10494.1, 10494.1, 10494.1, 10494.1, 10499.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 10494.1, 1 |                                         | L0803: 2, L0731: 2, H0580:<br>,, H0587: 1, 80005: 1,<br>,0369: 1, L0647: 1, L0666:<br>,, H0144: 1, H0520: 1,<br>80152: 1 and L0759: 1. | L0475; 1,0020; 1,0030; 1,0030; 1,0030; 1,0030; 2,1030; 2,1030; 2,1030; 2,1030; 2,1030; 2,1030; 2,1030; 2,1030; 2,1030; 2,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; 1,1030; |           | L0805: 2, H0619: 1, H0547: 7<br>and S0190: 1. |                                                                                  | S0442: 2                            | H0328: 1          |
| <u> </u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Arg-75 to Lys-81,<br>Gln-99 to Asp-109. | 2778                                                                                                                                   | Lys-71 to Trp-76.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |           | Pro-53 to Arg-59, I<br>Ala-64 to Cys-69. 1:   | Pro-13 to Ser-19,<br>Glu-25 to Glu-31,<br>Pro-44 to Gly-53,<br>Gly-74 to Arg-79. | Thr-45 to Pro-56, Ser-66 to Lys-74. | Thr-28 to Scr-40. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 732                                     | 575                                                                                                                                    | 576                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 733       | 217                                           | 734                                                                              | 278                                 | 579               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 57 - 422                                | 270 - 926                                                                                                                              | 307 - 534                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 306 - 455 | 257 - 526                                     | 420 - 656                                                                        | 166 - 429                           | 46 - 171          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 338                                     | 181                                                                                                                                    | 182                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 339       | 183                                           | 340                                                                              | 184                                 | 185               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 853373                                  | 700627                                                                                                                                 | 1352285                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 699848    | 1041383                                       | 897950                                                                           | 835049                              | 684307            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | HNTCE26                                 | HNTNC20                                                                                                                                | HNTNI01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HNTNI01   | HNTSY18                                       | HNTSY18                                                                          | HOCNF19                             | HODDF13           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         | 171                                                                                                                                    | 172                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |           | 173                                           |                                                                                  | 174                                 | 175               |

| (10,056.5, 8014.5, 10.78.4, 14.44.7, 10.48.6.5, 10.48.8, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, 10.75.4, | H0615: 1  | H0415: 1                                                                               |
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| 288                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 581       | 582                                                                                    |
| 434-541                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 358 - 489 | 49 - 1503                                                                              |
| 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 187       | 188                                                                                    |
| 422913                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 835027    | 1184465                                                                                |
| HODDN92                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HODEJ32   | НОЕМQ33                                                                                |
| 176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 177       | 178                                                                                    |

|                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                           |                   | -              | 51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                           |                   |                | L0564-9, 80250; 5, 80126: 15<br>3, 10.040; 1, 10.057; 3,<br>80360; 2, 10.051; 1, 10.11;<br>1, 80376; 1, 10.099; 1, 10.019;<br>1, 1. 0021; 1, 10.029; 1, 10.013;<br>1, 10.021; 1, 10.029; 1, 10.023;<br>1, 80081; 1, 10.022; 1, 10.023;<br>1, 80081; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.022; 1, 10.02 |
| Leu-252 to Glu-258,<br>Asp-280 to Thr-293,<br>Asp-280 to Thr-301,<br>Asp-321 to Asp-348,<br>Asp-363 to Ser-368,<br>His-370 to Thr-378,<br>Asp-390 to Cys-399,<br>Glu-391 to Cys-399,<br>Leu-421 to Arg-456,<br>Glu-491 to Arg-459, | Lear 7 to 69 44, The 157 to Leat 44, The 157 to Leat 44, Asy 194 to Val-201, Asy 208 to Th-238, Asy 208 to Th-239, Asy 208 to Sep-348, Asy 208 to Cys-348, Asy 208 to Cys-349, Lear 421, to Arg-459, | Leu-37 to Gly-43. | Met-2 to Ser-9 | Ghr.33 to Ghr.30,<br>Assa-42 to Ghy-65,<br>Thr-84 to Lys-100,<br>Ghr.103 to Ser.110,<br>Arg.132 to Phe-138,<br>Pro-159 to Arg-172.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                           | 736               | 737            | 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                    | 48 - 1502                                                                                                                                                                                                                                                                                                                                 | 78 - 875          | 124 - 741      | 170 - 724                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                    | 341                                                                                                                                                                                                                                                                                                                                       | 342               | 343            | 189                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                    | 968616                                                                                                                                                                                                                                                                                                                                    | 906694            | 902639         | 873264                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                    | НОРМОЗЗ                                                                                                                                                                                                                                                                                                                                   | HOFMQ33           | HOFMQ33        | HOHBY44                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                           |                   |                | 179                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

|                                               |         |                   |                      |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            | _                     |
|-----------------------------------------------|---------|-------------------|----------------------|-----------------------------------------------------|----------------------------|------------------------|----------------------------|-----------------------|---------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|------------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|
| L0773: 1, S0380: 1, S0350: 1<br>and S0026: 1. |         |                   | L0766: 12, L0758: 7, | 10616; 4, L0439; 4, L0754;<br>. r 0747; 4 r 0779; 4 | .0777; 4, L0601; 4, H0657; | , H0656: 3, H0081: 3,  | (0031; 3, H0038; 3, S0222; | , H0455: 2, H0618: 2, | 3617: 2, T0042: 2, H0494: | , S0210: 2, H0529: 2, | 0769: 2, L0662: 2, L0794: | , L0665: 2, H0445: 2, | (0543: 2, H0170: 1, H0394: | , H0556: 1, T0002: 1, | ,0029: 1, H0662: 1, S0358: | , S0045: 1, S0046: 1, S0140: | , L0717: 1, H0370: 1, | 10392: 1, H0497: 1, H0574: | , H0253: 1, H0318: 1, | I0597: 1, H0544: 1, H0545: | , H0178: 1, L0157: 1, | .0471: 1, S0050: 1, H0014: | , H0051: 1, T0010: 1, | I0408: 1, H0266: 1, H0188: | , H0290: 1, S0022: 1, | I0135: 1, H0090: 1, H0040: | , H0634: 1, H0264: 1, | .0448: 1, H0641: 1, S0142: | , S0344: 1, L0770: 1, | .0637: 1, L0645: 1, L0771: | , L0521: 1, L0768: 1, | .0803: 1, L0806: 1, L0805: | , L0652: 1, L0653: 1, | .0776: 1, L0655: 1, L0629: | , L0659: 1, L0789: 1, |
| 2 8                                           |         | Cys-25 to Asn-36. |                      | He-38 to Pro-46,   H                                |                            | Gly-110 to Ser-122, 3, |                            |                       | 1                         | ,<br>2                |                           | 2,                    | H                          | 1,                    | ×                          | 1,                           | 1,                    |                            | 1                     | 1                          | 1,                    |                            |                       | Ξ.                         | ,,                    |                            | 1,                    | <u>x</u>                   | 1,                    |                            | 1                     |                            |                       | 7                          |                       |
|                                               | 739     | 740               | 584                  |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |
|                                               | 2 - 232 | 54 - 305          | 361 - 852            |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |
|                                               | 345     | 346               | 190                  |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |
|                                               | 873263  | 785886            | 1352356              |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            | _                     |
|                                               | HOHBY44 | HOHBY44           | HOQBJ82              |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |
|                                               |         |                   | 180                  |                                                     |                            |                        |                            |                       |                           |                       |                           |                       |                            |                       |                            |                              |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |                            |                       |

| 0.0791: 1, L0663: 1, L0664:, H0519: 1, H0682: 1, H0539: 1, H0521: 1, H0539: 1, H0134: 1, H0134: 1, H0134: 1, H0134: 1, H0134: 1, H0422: 1, H0422: 1 and H0422: 1, H |                                                                                                          |           | S0418: 1, H0393: 1, S0003:<br>1, L0766: 1, L0804: 1 and<br>S0052: 1. | L0754; 4 L0799; 4, L0799; 1, L0754; 1, L0759; 2, L0779;  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Ser-30 to Met-36,<br>Ile-38 to Pro-46,<br>Gln-78 to Gly-88,<br>Thr-98 to Pro-105,<br>Gly-110 to Ser-122. |           | - 1 S                                                                | Gly-18 to Lys-23, 3 Pro-31 to Gly-38. 2 Gly-18 to Lys-23, 2 Gly-18 to Lys-23, 2 Gly-18 to Lys-23, 3 Gly-18 to Lys-23, 3 Gly-18 to Lys-23, 4 Gly-18 to Pro-30, 5 Gly-18 to Lys-23, 5 Gly-18 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 741                                                                                                      | 742       | 285                                                                  | 586<br>743<br>587                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 102 - 584                                                                                                | 55 - 1029 | 89 - 259                                                             | 1076 - 1195<br>146 - 268<br>508 - 3408                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 347                                                                                                      | 348       | 161                                                                  | 192<br>349<br>193                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 858338                                                                                                   | 857453    | 589431                                                               | 854234<br>566845<br>429229                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HOQBJ82                                                                                                  | HOQBJ82   | HOSBY40                                                              | HOSD125 HOSD125 HOUCQ17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                          |           | 181                                                                  | 183                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| 10014; 3, L0666; 3, L0663; | , S0126: 3, H0690: 3, | 0740: 3, L0752: 3, L0599: | , L0361: 3, H0713: 2, | (0212: 2, H0427: 2, S0280: | , H0544: 2, S0003: 2, | 10644: 2, L0598: 2, L0649: | , L0803: 2, L0657: 2, | 0659: 2. L0809: 2. L3872: | 10789: 2 10438: 2 | 2 H0479, 2 L0744. | 0406; 2, H04/8; 2, L0/44; | L0754: 2, L0756: 2, | 0779: 2, L0757: 2, L0758: | . H0667: 2, S0276: 2, | 0739: 1. H0624: 1. H0170: | H0171-1 S0040-1 | 00005, 1 F 2402, 1 C0354, | 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1 | . S0358: 1, S0444: 1, S0360: | , S0408: 1, L1441: 1, | 0730: 1, H0734: 1, S6022: | , H0587: 1, H0486: 1, | 0039: 1, L3506: 1, L3530: | H0599: 1, H0036: 1, | 0010: 1. H0545: 1. L0471: | L0163: 1, H0687: 1. | 0250: 1, L0483: 1, H0030: | H0553: 1, L0142: 1, | 10617: 1, H0616: 1, T0067: | , H0380: 1, H0100: 1, | .0494: 1, S0210: 1, | NKWN: 1, L0769: 1, | .3904: 1, L5565: 1, L0643: | L0767; 1, L0774; 1, | 0775: 1. L0375: 1. L0784: | . L0776; 1, L0656; 1. | 4669; 1, L0783; 1, L0384; | .L5622: 1, L2259: 1. | 10693: 1, H0724: 1, H0520: | . H0670; 1, H0648; 1, |
|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-------------------|-------------------|---------------------------|---------------------|---------------------------|-----------------------|---------------------------|-----------------|---------------------------|------------------------------------------|------------------------------|-----------------------|---------------------------|-----------------------|---------------------------|---------------------|---------------------------|---------------------|---------------------------|---------------------|----------------------------|-----------------------|---------------------|--------------------|----------------------------|---------------------|---------------------------|-----------------------|---------------------------|----------------------|----------------------------|-----------------------|
| H0014:                     | 3, S012               | L0740:                    | 3, L036               | 80212::                    | 2, H054               | H0644:                     | 2, L080               | 1.0659                    | 8101              | 500405            | 20406                     | Z, L075             | E0779:                    | 2. H066               | H0739                     | H012            | 10101                     | 1 0025                                   | 1, 5035                      | 1, S040               | H0730:                    | 1, H058               | T0039:                    | 1, H059             | 30010:                    | I. L016             | 80250:                    | 1, H055             | H0617:                     | 1, H038               | H0494:              | UNKW               | L3904:                     | 1. L076             | L0775:                    | I. L077               | L4669:                    | 1, L562              | H0693:                     | 1. H067               |
|                            |                       |                           |                       |                            |                       |                            |                       |                           |                   |                   |                           |                     |                           |                       |                           |                 |                           |                                          |                              |                       |                           |                       |                           |                     |                           |                     |                           |                     |                            |                       |                     |                    |                            |                     |                           |                       |                           |                      |                            |                       |
|                            |                       |                           |                       |                            |                       |                            |                       |                           |                   | _                 |                           | _                   |                           |                       |                           | _               |                           |                                          | _                            |                       |                           |                       |                           |                     |                           |                     |                           |                     |                            |                       |                     |                    |                            |                     |                           |                       |                           |                      |                            |                       |
|                            |                       |                           |                       |                            |                       |                            |                       |                           |                   |                   |                           |                     |                           |                       |                           |                 |                           |                                          |                              |                       |                           |                       |                           |                     |                           |                     |                           |                     |                            |                       |                     |                    |                            |                     |                           |                       |                           |                      |                            |                       |

|                                                                                                        |                                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        |                   |                  |                   |                    |                    |                     |                   | 4,8       |           |            |           | 10,2                            |                        |                            |                        |                 |                   |                   |
|--------------------------------------------------------------------------------------------------------|----------------------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|------------------------|-------------------|------------------|-------------------|--------------------|--------------------|---------------------|-------------------|-----------|-----------|------------|-----------|---------------------------------|------------------------|----------------------------|------------------------|-----------------|-------------------|-------------------|
| H0672: 1, S0044: 1, L0777: 1, L0755: 1, L0759: 1, S0031: 1, S0260: 1, S0192: 1, S0242: 1 and S0196: 1. | H0165:1                                | L0747: 8, L0749: 5, L0755: | 5, H0013: 3, L0769: 3, | L0731: 3, S0212: 2, L0770: | 2, L0803: 2, H0144: 2, | L0756: 2, H0624: 1, H0171: | 1, S0282: 1, H0776: 1, | H0592: 1, H0427: 1, H0575: | 1, H0041: 1, H0124: 1, | H0163: 1, H0038: 1, L0637: | 1, L0774: 1, L0775: 1, | L0791: 1, H0648: 1, H0756: | 1. S0028: 1. L0439: 1. | L0777: 1 and S0436: 1. |                   |                  |                   |                    |                    |                     | S0152: 1          | S0152: 2  |           |            |           | H0619: 2, H0484: 1, H0600: 10,2 | 1, H0553: 1, H0056: 1, | LU/66: 1, LU663: 1, HU693: | 1, H0393; 1, 30132; 1, | 1 and H0423: 1. |                   |                   |
|                                                                                                        | Lys-16 to Ser-21,<br>Gly-36 to Asp-41. | Asp-40 to Glu-50,          | Ser-59 to Gly-69,      | Leu-109 to Lys-117,        | Tyr-130 to Leu-137,    | Leu-140 to Glu-160,        | Gly-202 to Tyr-208.    |                            |                        |                            |                        |                            |                        |                        | Asp-40 to Glu-50, | Ser-59 to Glv-69 | Ala-98 to His-105 | Arg-108 to Ghr-114 | Pro-124 to Cor-138 | Ala-143 to Giv-154. | Arg-30 to Gln-36. |           |           |            |           | Arg-50 to Leu-56.               |                        |                            |                        |                 | Arg-50 to Leu-56. | Thr-43 to Asp-59, |
| 000                                                                                                    | 288                                    | 589                        |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        | 744               |                  |                   |                    |                    |                     | 290               | 591       | 745       | 746        | 747       | 592                             |                        |                            |                        |                 | 748               | 749               |
|                                                                                                        | 51 - 176                               | 128 - 763                  |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        | 127 - 648         |                  |                   |                    |                    |                     | 236 - 397         | 126 - 272 | 119 - 265 | 1001 - 696 | 509 - 523 | 86 - 325                        |                        |                            |                        |                 | 136 - 378         | 232 - 666         |
|                                                                                                        | 194                                    | 195                        |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        | 350               |                  |                   |                    |                    |                     | 961               | 161       | 351       | 352        | 353       | 198                             |                        |                            |                        |                 | 354               | 355               |
|                                                                                                        | 520202                                 | 1310868                    |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        | 590741            |                  |                   |                    |                    |                     | 669589            | 1011467   | 525375    | 796925     | 285669    | 1146674                         |                        |                            |                        |                 | 1034817           | 1046434           |
| 0.000                                                                                                  | HPEAD79                                | HPIB015                    |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        | HPIB015           |                  |                   |                    |                    |                     | HPJBI33           | HPJBK12   | HPJBK12   | HPJBK12    | HPJBK12   | HPJCL22                         |                        |                            |                        |                 | HPJCL22           | HPJCL22           |
|                                                                                                        | 184                                    | 185                        |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                        |                   |                  |                   |                    |                    |                     | 186               | 187       |           |            |           | 188                             |                        |                            |                        |                 |                   |                   |

|                                         |                                                                                   |                                                    |                       | _                                                 | _                          |                       | _                                                 | _                          | _                     | _                         | _                     |                                               | _                         | _                     | _                          | _                     | _                            | _                          | _                     | _                          | _                     | _               | _                         | _                   | _                            | _                         | _                     | _                          | _                                                        |
|-----------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------|-----------------------|---------------------------------------------------|----------------------------|-----------------------|---------------------------------------------------|----------------------------|-----------------------|---------------------------|-----------------------|-----------------------------------------------|---------------------------|-----------------------|----------------------------|-----------------------|------------------------------|----------------------------|-----------------------|----------------------------|-----------------------|-----------------|---------------------------|---------------------|------------------------------|---------------------------|-----------------------|----------------------------|----------------------------------------------------------|
|                                         |                                                                                   |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         |                                                                                   |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         |                                                                                   |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | 55 13                                                                             |                                                    |                       | 7:                                                | ÷                          | _                     |                                                   | -:                         |                       | ë                         | ,                     | ÷                                             |                           |                       |                            |                       | -f                           |                            | _                     | <u></u>                    | _                     | _               |                           | _                   | 1.                           |                           |                       | . · · ·                    | .e                                                       |
|                                         | S0358: 5, L0809: 4, L0742:<br>, L0743: 4, L0590: 4,<br>10543: 4, S0360: 3, H0031: | , S0422: 3, L0763: 3,<br>0764: 3 1 0766: 3 1 0754- | 33:2,                 | 10266: 2, H0617: 2, L4497:<br>1.0769: 2-1.0776: 2 | 10658: 2, H0696: 2, L0748: | 15: 2,                | 0454: 2, S0110: 1, H0665:<br>1 0481 · 1 H0730 · 1 | 10747: 1, H0411: 1, H0431: | 74: 1,                | 10632: 1, L2490: 1, H0253 | 46: I,                | H0012-1, H0150: 1, H0123:<br>H0012-1, S0050-1 | 0051: 1, H0188: 1, S0003: | 96: 1,                | 10606: 1, H0673: 1, H0090: | 12: 1,                | 70069: 1, S0112: 1, S0344: 1 | 10538: 1, H0529: 1, L0770: | 2: 1,                 | .0768: 1, L0794: 1, L0560: | 0517-1 10540-1 10384- | 1,1000          | 0665: 1. L2260: 1. L2654: | 1.                  | .3832: 1, S0004: 1, S0390: 1 | 3014: 1, L0439: 1, L0740: | 6: 1,                 | .0779: 1, S0436: 1, L0480: | , L0596; 1, S0026; 1, S0276;<br>, S0196; 1, L2854; 1 and |
|                                         | S0358: 5, L0809: 4, L<br>1, L0743: 4, L0590: 4,<br>10543: 4, S0360: 3, H0         | , S0422: 3, L0763: 3,<br>0764: 3 1 0766: 3 1 0     | , H0716: 2, H0333: 2, | 10266: 2, H0617: 2, L4<br>1.0769: 2, 1.0776: 2    | , H0696                    | , L0749: 2, H0445: 2, | 0454: 2, S0110: 1, HU<br>1 0481: 1 H0730: 1       | H0411                      | , H0370: 1, H0574: 1, | , L2490:                  | , H0052: 1, H0546: 1, | H0012-1 S0050-1                               | H0188                     | , H0428: 1, T0006: 1, | l, H0673                   | , H0040: 1, H0412: 1, | , S0112:                     | l, H0529                   | , L0761: 1, L0662: 1, | 0768: 1, L0794: 1, L0      | 1, 5000               | 15622-1 10666-1 | L2260:                    | S0374: 1, H0684: 1, | , S0004:                     | , L0439;                  | , L0747: 1, L0756: 1, | , S0436:                   | 1, S002                                                  |
|                                         | S0358:<br>4, L0743<br>H0543: 4                                                    | 3, S0422                                           | 3, H0716              | H0266: 2                                          | H0658: 2                   | 2, L0749              | S0454: 2                                          | H0747: 1                   | 1, H0370              | H0632: 1                  | 1, H005               | H0545:                                        | S0051: 1                  | 1, H0428              | H0606: 1                   | 1, H004C              | T0009: 1                     | H0538: 1                   | 1, L0761              | L0768: 1                   | 1, 20//2              | 1 15622         | L0665: 1                  | 1, S0374            | L3832: 1                     | S3014: 1                  | 1, L0747              | L0779: 1                   | 1, L05%<br>1, S0196                                      |
|                                         |                                                                                   | . 20                                               | · ··                  |                                                   | i                          |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
| Gly-94,                                 | Asn-86,<br>Met-71,<br>Asn-86.                                                     | Asp-110<br>Cvs-13                                  | Glu-15                | Arg-19                                            |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
| Gly-88 to Gly-94,<br>Lvs-105 to Ilc-115 | Ala-55 to Asn-60,<br>Lys-65 to Met-71,<br>Leu-75 to Asn-86,                       | Asp-93 to Asp-110,                                 | Gln-149 to Glu-154,   | Thr-172 to Ilc-179,<br>Ghr-185 to Arg-192         |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | 293 /                                                                             |                                                    |                       |                                                   | <u></u>                    |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         |                                                                                   |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | 64 - 669                                                                          |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | 661                                                                               |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         |                                                                                   |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | 846357                                                                            |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | HPMDK28                                                                           |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | HPM                                                                               |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |
|                                         | 189                                                                               |                                                    |                       |                                                   |                            |                       |                                                   |                            |                       |                           |                       |                                               |                           |                       |                            |                       |                              |                            |                       |                            |                       |                 |                           |                     |                              |                           |                       |                            |                                                          |

| $\overline{}$ |         |     |           |     |                      | L3612: 1.                     |  |
|---------------|---------|-----|-----------|-----|----------------------|-------------------------------|--|
|               | 639118  | 356 | 58 - 663  | 750 | Ala-55 to Asn-60,    |                               |  |
| _             |         |     |           |     | Lys-65 to Met-71,    |                               |  |
| _             |         |     |           |     | Leu-75 to Asn-86,    |                               |  |
|               |         |     |           |     | Asp-93 to Asp-110,   |                               |  |
|               |         |     |           |     | Cir. 140 to Cys-138, |                               |  |
| _             |         |     |           |     | Thr-172 to Ile-179   |                               |  |
|               |         |     |           |     | Glu-185 to Arg-192.  |                               |  |
| Г             | 1352342 | 200 | 62 - 1321 | 594 | Pro-31 to Thr-48,    | H0694: 5, L0759: 5, L0766: 3  |  |
|               |         |     |           |     | Arg-62 to Gly-70,    | 4, H0261: 3, S0222: 3,        |  |
| _             |         |     |           |     | Ala-74 to Glu-87,    | H0486: 3, H0052: 3, L0731:    |  |
| Т             |         |     |           |     | Lys-123 to Asp-129,  | 3, L3316: 2, H0252: 2,        |  |
| Т             |         |     |           |     | Pro-162 to Gly-167,  | L0764: 2, L0662: 2, L0775:    |  |
| Т             |         |     |           |     | Glu-170 to Gly-189,  | 2, L0657; 2, L0659; 2,        |  |
| _             |         |     |           |     | Arg-220 to Asn-228,  | L0530: 2, L0666: 2, L0748:    |  |
| Т             |         |     |           |     | Glu-248 to Ala-258,  | 2, L0439; 2, L0750; 2,        |  |
|               |         |     |           |     | Gly-285 to Gly-300,  | L0588: 2, L0594: 2, H0224:    |  |
| Т             |         |     |           |     | Pro-315 to Glv-327.  | 1. H0717: 1. H0656: 1.        |  |
|               |         |     |           |     | Ser-406 to Arg-411.  | S0001: 1, S0360: 1, S0408: 1, |  |
|               |         |     |           |     | •                    | H0729: 1, S0045: 1, H0619:    |  |
| _             |         |     |           |     |                      | 1, L3388: 1, H0592: 1,        |  |
|               |         |     |           |     |                      | H0587: 1, H0333: 1, S0474:    |  |
| _             |         |     |           |     |                      | 1, H0014: 1, L0163: 1,        |  |
|               |         |     |           |     |                      | H0051: 1, H0355: 1, T0006:    |  |
| _             |         |     |           |     |                      | 1, H0644: 1, H0032: 1,        |  |
| _             |         |     |           |     |                      | H0212: 1, L0456: 1, H0124:    |  |
|               |         |     |           |     |                      | 1, H0708: 1, S0036: 1,        |  |
| _             |         |     |           |     |                      | H0038: 1, H0616: 1, H0087:    |  |
| _             |         |     |           |     |                      | 1, H0059: 1, H0280: 1,        |  |
|               |         |     |           |     |                      | S0440: 1, S0150: 1, H0633:    |  |
| _             |         |     |           |     |                      | 1, L0369: 1, L0763: 1,        |  |
|               |         |     |           |     |                      | L0769: 1, L0638: 1, L0637:    |  |
| _             |         |     |           |     |                      | 1, L5566: 1, L0761: 1,        |  |
|               |         |     |           |     |                      | L0772: 1, L0648: 1, L0803:    |  |
| _             |         |     |           |     |                      | 1, L0650: 1, L0805: 1,        |  |
|               |         |     |           |     |                      | L0809: 1, L0647: 1, L0665:    |  |
|               |         |     |           |     |                      | 1, H0539: 1, H0521: 1,        |  |
|               |         |     |           |     |                      | H0696: 1, H0555: 1, L0754:    |  |

| , L0749: 1, L0753: 1,<br>L0755: 1, L0757: 1, L0605:<br>1, L0599: 1 and L3352: 1, |                                                                                                                                       |                   | H0555: 1                                                                         |                                                                                  | H0556. Is 10252. 8. 1.0766. 2. 1.0805. 1. 1.0766. 2. 1.0805. 2. 1.0766. 1.0805. 3. 1.0766. 4. 10554. 4. 1.0769. 4. 10554. 4. 1.0799. 4. 10554. 4. 1.0799. 4. 10554. 4. 1.0799. 4. 10559. 4. 1.0799. 4. 10559. 4. 1.0799. 4. 10559. 4. 1.0799. 4. 10559. 4. 1.0799. 5. 10566. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 4. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. 10569. 5. 1.0799. 5. |
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|                                                                                  | Pro-31 to Thr-48, Ala-74 to Glu-87, Ala-74 to Glu-87, Lys-123 to Asp-129, Pro-162 to Gly-167, Glu-170 to Gly-189, Arg-220 to Asn-228. | Ser-49 to Arg-54. | Ala-30 to Gly-36,<br>Asp-45 to Trp-50,<br>Lys-65 to Cys-71,<br>Pro-80 to Cys-87. | Ala-30 to Gly-36,<br>Asp-45 to Trp-50,<br>Lys-65 to Cys-71,<br>Pro-80 to Cys-87. | <u> </u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                  | 751                                                                                                                                   | 752               | 295                                                                              | 753                                                                              | 996                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                  | 70 - 1245                                                                                                                             | 148 - 339         | 144 - 452                                                                        | 130 - 438                                                                        | 252 - 410                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                  | 357                                                                                                                                   | 358               | 201                                                                              | 359                                                                              | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                  | 844216                                                                                                                                | 484735            | 882176                                                                           | 588460                                                                           | 871221                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                  | HPRAL78                                                                                                                               | HPRAL78           | HRABA80                                                                          | HRABA80                                                                          | HRACDIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                  |                                                                                                                                       |                   | 161                                                                              |                                                                                  | 192                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | l         |                                                                                                               |
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| 1,1039; 1,1049; 1,1040; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,1049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,049; 1,0 |           | L0731: 11, L0803: 7,<br>L0748: 7, L0517: 6, L0809:<br>6, L0749: 6, L0439: 5,<br>S0410: 4, S0002: 4, L0770: 4, |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           | Arg-31 to Lys-37,<br>Lys-58 to Glu-65,<br>Asp-157 to Gly-168,<br>Ile-219 to Gly-225,                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 754       | 597                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 252 - 413 | 132 - 1550                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 360       | 203                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 706332    | 877666                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HRACD15   | HRACJ35                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           | 193                                                                                                           |

| 0.094-6.1388; 4.1212.  (3.404-6.1388; 4.1212.  (3.404-6.1388; 1.1047.  (1.075:3.1009.3.1.077.  (1.075:3.1009.3.1.077.  (1.075:3.1009.3.1.077.  (2.1004-2.1.005.2.1.077.  (3.404-6.1.005.3.1.077.  (3.404-6.1.005.3.1.007.  (3.404-6.1.005.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (3.404-6.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.007.  (4.406-6.1.1.007.1.1.1.1.007.  (4.406-6.1.1.007.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1 |                                                                                                                                  |                  |
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| Ala-260 to Ser-266. Thr-276 to Glu-282.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Arg-31 to Lys-37,<br>Lys-58 to Glu-65,<br>Asp-157 to Gly-168,<br>Ho-219 to Gly-225,<br>Ala-260 to Ser-268,<br>Thr-276 to Glu-282 | Ile-9 to Gly-15, |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 755                                                                                                                              | 756              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 99 - 1517                                                                                                                        | 1 - 534          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 361                                                                                                                              | 362              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 730504                                                                                                                           | 470546           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | HRAC135                                                                                                                          | HRACJ35          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                  |                  |

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|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------------------------|-------------------------------------------------------|------------------------|-----------------------------------------------|-------------------|--------------------------------------------|---------|-------------------|----------------------------|------------------------|------------------------|---------------------|-------------------|-------------------|--------------------------------------------|-------------------|-------------------|---------------------|----------------------------|------------------------------------------------------|----------------------------|------------------------|----------------------------|------------------------|------------------------------------------------------|
|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                        |                            |                                                       |                        |                                               |                   |                                            |         |                   |                            |                        |                        |                     |                   |                   |                                            |                   |                   |                     |                            |                                                      |                            |                        |                            |                        |                                                      |
|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                        |                            |                                                       |                        |                                               |                   |                                            |         |                   | 3:                         |                        |                        |                     |                   |                   |                                            |                   |                   |                     | 36                         | ŕ                                                    |                            | _                      |                            |                        |                                                      |
|                                        | L0655: 4, H0650: 2, H0657: 2, H0656: 2, H0656: 2, H0656: 2, H0656: 2, H0656: 2, H0656: 3, H0666: | 2, H0306: 1, S0408: 1, | H0318: 1, H0046: 1, H0266: | 1, S0038: 1, H0429: 1,<br>H0560: 1, S0344: 1, 1,0789: | 1, S0053: 1, H0689: 1, | H0134: 1, L0779: 1, L0777: 1<br>and H0445: 1. |                   |                                            |         |                   | H0316: 1, L3905: 1, L0565: | 1, L0438: 1, H0521: 1, | L0439: 1 and L0594: 1. |                     |                   |                   |                                            |                   |                   |                     | L0509: 9, L0766: 4, L0515: | 2, E0763: 2, 30342: 1, 30114:<br>1 S0218: 1 H0589: 1 | H0645: 1. H0592: 1. H0250: | 1. H0581; 1. H0057; 1. | H0252: 1, H0328: 1, H0674: | 1, H0598: 1, H0090: 1, | H0634: 1, H0488: 1, H0625:<br>1, S0426: 1, L0506: 1, |
| Ala-50 to Ser-58,<br>Thr-66 to Glu-72. | Thr-48 to Arg-56,<br>Pro-122 to Glu-127,<br>Lys-135 to Cys-143,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Ala-230 to Tyr-238,    | Thr-244 to Gln-255,        | Pro-274 to Ser-279,<br>Thr-284 to Phe-306             | Leu-345 to Thr-354.    |                                               | Thr-48 to Arg-56, | Pro-122 to Glu-127,<br>Ala-136 to Tyr-141. |         | Pro-24 to Arg-32. | lle-4 to Tyr-10,           | Arg-119 to Pro-126,    | Glu-152 to Gly-158,    | Thr-209 to Phe-215. | Arg-40 to Pro-47, | Glu-73 to Gly-79, | Thr-130 to Phe-136,<br>Lvs-277 to Lvs-283. | Arg-40 to Pro-47. | Glu-73 to Gly-79, | Thr-130 to Phe-136. | Thr-19 to Thr-25.          |                                                      |                            |                        |                            |                        |                                                      |
|                                        | 865                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                            |                                                       |                        |                                               | 757               |                                            | 758     | 759               | 599                        |                        |                        |                     | 092               |                   |                                            | 761               |                   |                     | 009                        |                                                      |                            |                        |                            |                        |                                                      |
|                                        | 30 - 1109                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                        |                            |                                                       |                        |                                               | 30 - 626          |                                            | 11 - 19 | 1048 - 1146       | 10 - 1146                  |                        |                        |                     | 31 - 879          |                   |                                            | 247 - 1104        |                   |                     | 122 - 268                  |                                                      |                            |                        |                            |                        |                                                      |
|                                        | 204                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                            |                                                       |                        |                                               | 363               |                                            | 364     | 365               | 205                        |                        |                        |                     | 366               |                   |                                            | 367               |                   |                     | 506                        |                                                      |                            |                        |                            |                        |                                                      |
|                                        | 910133                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                        |                            |                                                       |                        |                                               | 904040            |                                            | 904621  | 863802            | 1181699                    |                        |                        |                     | 1114849           |                   |                                            | 1027712           |                   |                     | 827306                     |                                                      |                            |                        |                            |                        |                                                      |
|                                        | HRGBL78                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                        |                            |                                                       |                        |                                               | HRGBL78           |                                            | HRGBL78 | HRGBL78           | HROAJ39                    |                        |                        |                     | HROAJ39           |                   |                                            | HROAJ39           |                   |                     | HROBD68                    |                                                      |                            |                        |                            |                        |                                                      |
|                                        | 194                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                            |                                                       |                        |                                               |                   |                                            |         |                   | 195                        |                        |                        |                     |                   |                   |                                            |                   |                   |                     | 196                        |                                                      |                            |                        |                            |                        |                                                      |

| L0667: 1, L0499: 1, L0803: 1, L0499: 1, L0514: 1, L0514: 1, L0511: 1, L0809: 1, 80052: 1, 80428: 1, H0683: 1, 80152: 1, 80156: 1, L0748: 1, L0575: 1, L0759: 1, L0599: 1 and H0543: 1. | H0068: 3, S0114: 2, L0534: 7<br>2, L0740: 2, H0717: 1,<br>S0134: 1, S042: 1, S0354: 1,<br>S0476: 1, H0333: 1, H0009:<br>1, H0560: 1, L5565: 1 and |                                        | 100011, 1,0059, 1,0039, 1,0039, 1,0039, 1,0039, 1,0039, 1,0038, 3,0036, 1,0038, 3,0036, 1,0038, 3,0036, 1,0038, 3,0036, 1,0038, 3,0036, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038, 1,0038 |                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
|                                                                                                                                                                                        | Leu-S1 to Gly-77,<br>Re-117 to Pro-125.                                                                                                           | Thr-25 to Cys-30,<br>Pro-35 to Arg-42. | Vala29a vala37,<br>App-71 to His-76,<br>Glp-78 to Gly-84,<br>Mectof So His-110,<br>Trp-117 to Ara-123,<br>U-8a-77 to Abs-244,<br>Trm-256 to Asp-224,<br>Ever-275 to Lys-230,<br>Ser-275 to Lys-230,<br>Gly-28 to Gly-331,<br>Gly-28 to Gly-331,<br>Gly-28 to Gly-331,<br>Gly-28 to Gly-331,<br>Gly-28 to Gly-332,<br>Cys-343 to Asp-359.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Val-29 to Val-37, |
|                                                                                                                                                                                        | 109                                                                                                                                               | 762                                    | 602                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 763               |
|                                                                                                                                                                                        | 142 - 570                                                                                                                                         | 122 - 256                              | 60 - 1256                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 126 - 1043        |
|                                                                                                                                                                                        | 207                                                                                                                                               | 368                                    | 208                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 369               |
|                                                                                                                                                                                        | 460527                                                                                                                                            | 371416                                 | 1352253                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 866579            |
|                                                                                                                                                                                        | HSAWD74                                                                                                                                           | HSAWD74                                | HSDEK49                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HSDEK49           |
|                                                                                                                                                                                        | 197                                                                                                                                               |                                        | 861                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                   |

|                                                                                                                                                                                                                                | 8,0026, 6,3016, 4, L075, 5, 2014, 2, L076, 2, L084, 5, 2014, 2, L084, 5, L084, 5, L086, 5, L096, 5, L0 |
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| Asp-71 to His-76,<br>Gln-78 to Giy-84,<br>Met-105 to His-110,<br>Trp-117 to Gly-122,<br>Gln-136 to Lys-441,<br>Trn-120 to Asp-174,<br>Sec-181 to Lys-186,<br>Gln-221 to Gln-228,<br>Gln-221 to Gln-228,<br>Gln-221 to Gln-228, | Alacji to Ghedji. Asprča Sarryj. Asprča Sarryj. Leu-164 to Ghedji. Ghe-171 to Lys-201.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                | 603                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                | 99 - 767                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                | 209                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                | 834619                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                | HSDF126                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                | 661                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                             |                                          | S0360: 1, L0794: 1, L0759:<br>and S0260: 1. | L0803: 14, L0774: 4,<br>20770: 2, H0409: 1, H0331:<br>and H0555: 1. |                                        | 10795; 6 8022; 4 10803; 10705; 6 8022; 4 10803; 10706; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; 3 1066; | H0036: 1 and L0744: 1. | S0356: 14, S0212: 4, S0040:<br>7, H0599: 2, H0551: 2,<br>H0413: 2, S0210: 2, S0126: |
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|                                                             |                                          | SO E                                        | 1 CO.                                                               |                                        | 1, 10, 10, 10, 10, 10, 10, 10, 10, 10, 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HO                     | 30.<br>H0H                                                                          |
| Ala-21 to Glu-31,<br>Thr-37 to Cys-43,<br>Pro-64 to Asp-69. | Thr-32 to Lys-40,<br>Lys-146 to Glu-152. |                                             | Glu-33 to Glu-56,<br>Thr-75 to Cys-81.                              | Glu-33 to Glu-56,<br>Thr-75 to Cys-81. | Lea-23 to Met-30.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Glu-37 to Gly-45.      | Gly-16 to Arg-32,<br>Ala-42 to Asn-50,<br>Glu-66 to Gln-76,                         |
| 764                                                         | 604                                      | 909                                         | 909                                                                 | 765                                    | 607                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 809                    | 609                                                                                 |
| 99 - 317                                                    | 247 - 705                                | 351 - 473                                   | 16 - 423                                                            | 22 - 387                               | 177 - 392                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 8 - 184                | 41 - 586                                                                            |
| 370                                                         | 210                                      | 211                                         | 212                                                                 | 371                                    | 213                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 214                    | 215                                                                                 |
| 836071                                                      | 795252                                   | 491112                                      | 1301498                                                             | 463645                                 | 612823                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 589447                 | 1304677                                                                             |
| HSDFJ26                                                     | HSDJA15                                  | HSDJM31                                     | HSDSB09                                                             | HSDSB09                                | нянахгі                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HSIDJ81                | HSJBQ79                                                                             |
|                                                             | 200                                      | 201                                         | 202                                                                 |                                        | 203                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 204                    | 205                                                                                 |

| E, 80027, 2, 106-65; 2, 80027, 2, 1106-65; 2, 80027, 2, 1107-64; 8048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9048, 9 |                                                                                                                                                                                                                                                   |                                                                                                                                | 80212: 13, 80126: 12, 10077: 11, 80027: 10, 8028: 10, 802077: 11, 80027: 6, 80360: 8, 800225; 8, 800225; 8, 80025; 8, 80194: 5, 80194: 5, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4, 40731: 4 |
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| Arg-88 to Gly-94, The-108 to Gly-118, The-121 to Gly-130, Leu-175 to Hs-14, Gli-155 to Lys-161, Asp-175 to Ser-180.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | (dy-16 ox Age-27,<br>Ala-42 to Age-30,<br>Glu-66 to Glu-76,<br>Age-85 to Glu-76,<br>The 121 to Gly-130,<br>Len-137 to His-144,<br>Glu-137 to His-144,<br>Glu-137 to Gly-130,<br>Glu-230 to Gly-217,<br>Glu-232 to Glu-237,<br>The-248 to Age-295, | Gly-16 to Arg-32,<br>Ala-42 to Asn-50,<br>Glu-66 to Gln-76,<br>Arg-85 to Gly-94,<br>Thr-108 to Asp-115,<br>Trp-121 to Gly-130. | Gly-31 to Arg-36,<br>Thr-55 to Glu-62,<br>Ser-64 to Ser-79,<br>Arg-103 to Ala-109,<br>Asp-120 to Ala-109,<br>Asp-120 to Arg-126,<br>Gly-294 to Gly-302,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| , н0713: 3, н0716: 3,  | S0444: 3, H0599: 3, L0163: | , S0210: 3, L0807: 3, S0390: | , S0037: 3, S3014: 3, L0740: | , S0192: 3, H0295: 2, | 10486: 2, H0706: 2, H0309: | H0023: 2, H0373: 2, | 10266: 2, H0039: 2, H0038: | L0598: 2, L3872: 2,    | 10689; 2, L0757; 2, L0759; | L0599; 2, S0011; 2, S0040; | L2906: 1, S0298: 1, | 0661: 1, H0663: 1, H0662: | , S0420: 1, S0356: 1, S0442: | S0408; 1, L2338; 1, S0046; | H0411; 1, H0550; 1, | 10586; 1, H0587; 1, H0333; | T0040: 1, T0060: 1,    | 10427: 1, H0251: 1, H0150: | H0050: 1, H0014: 1,    | 10188: 1, S0214: 1, H0428: | , H0622: 1, T0006: 1, | 0553: 1, H0628: 1, H0124: | , H0087: 1, H0551: 1, | 0067: 1, H0413: 1, T0069: | S0440: 1, L0762: 1, | 0763: 1, L0770: 1, L0769: | , L0637: 1, L0773: 1, | .0768: 1, L0794: 1, L0386: | L0774: 1, L0775: 1, | .0375: 1, L0805: 1, L0776: | , L0655: 1, L0783: 1, | 0519: 1, L0367: 1, L0790: | L0666: 1, L0663: 1, | 2263: 1, L0565: 1, S0148: | , H0726: 1, H0724: 1, | .0438: 1, H0519: 1, S0152: | , S0454: 1, H0521: 1, |
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| Ser-305 to Ala-318, 4, | Val-320 to Arg-327, SC     | 9                            | Thr-383 to Thr-399, 3,       | Θ.                    | Ξ.                         |                     | Ξ.                         | Ser-503 to Arg-514, 2, | Ξ.                         | _ci                        |                     | Asn-667 to Lys-672, Hi    |                              | _                          | _                   | Ξ.                         | Lys-871 to Met-883, 1, | Pro-914 to Tyr-923, Hi     | Ser-925 to Arg-939, 1, | Ξ                          |                       | <u> </u>                  |                       |                           |                     |                           |                       |                            |                     | <u> </u>                   | ,                     |                           |                     |                           | <u>-</u>              |                            |                       |
|                        |                            |                              |                              |                       |                            |                     |                            |                        |                            |                            |                     |                           |                              |                            |                     |                            |                        |                            |                        |                            |                       |                           |                       |                           |                     |                           |                       |                            |                     |                            |                       |                           |                     |                           |                       |                            |                       |
|                        |                            |                              |                              |                       |                            |                     |                            |                        |                            |                            |                     |                           |                              |                            |                     |                            |                        |                            |                        |                            |                       |                           |                       |                           |                     |                           |                       |                            |                     |                            |                       |                           |                     |                           |                       |                            |                       |
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| 1, L0439: 1, L0750: 1,<br>H0595: 1, S0436: 1, H0668:<br>1, H0667: 1, S0242: 1,<br>S0276: 1 and L3603: 1, |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                            | H0556: 14, L0666: 5, |
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|                                                                                                          | (dly-31 to Arg-36,<br>Thr-55 to Glit-22,<br>Ser-64 to Ser-79,<br>Arg-105 to Asp-106,<br>Asp-120 to Asp-126,<br>Asp-120 to Arg-126,<br>Asp-130 to Arg-312,<br>Ser-305 to Arg-318,<br>Pro-34-20 Thr-351,<br>Thr-353 to Thr-351,<br>Thr-364 to Lys-435,<br>Gly-461 to Asp-435,<br>Gly-461 to Asp-435,<br>Gly-461 to Asp-435,<br>Gly-461 to Asp-435,<br>Gly-461 to Asp-435,<br>Gly-461 to Asp-435,<br>Gly-461 to Asp-435, | (dby-27) to Arg-23. Thre-51 to Gla-8. Ser-60 to Ser-75. Ser-60 to Ser-75. Arg-83 to Asp-92. Arg-83 to Asp-92. Arg-93 to Asp-92. Arg-93 to Arg-12. Oby-29 to Arg-14. Thr-58 to Arg-345. Thr-58 to Hag-345. Thr-58 to Hag-375. Arg-010 Ser-446. Thr-47 to Ser-446. Thr-47 to Arg-370 to Ser-476. Gly-481 to Gli-496. Ser-50 to Arg-77. Gly-481 to Gli-496. Ser-50 to Arg-77. | He-60 to Asn-69,     |
|                                                                                                          | 768                                                                                                                                                                                                                                                                                                                                                                                                                   | 769                                                                                                                                                                                                                                                                                                                                                                        | 611                  |
|                                                                                                          | 127 - 1653                                                                                                                                                                                                                                                                                                                                                                                                            | 12 - 1673                                                                                                                                                                                                                                                                                                                                                                  | 353 - 1132           |
|                                                                                                          | 374                                                                                                                                                                                                                                                                                                                                                                                                                   | 375                                                                                                                                                                                                                                                                                                                                                                        | 217                  |
|                                                                                                          | 1074734                                                                                                                                                                                                                                                                                                                                                                                                               | 872570                                                                                                                                                                                                                                                                                                                                                                     | 676075               |
|                                                                                                          | HSK DA27                                                                                                                                                                                                                                                                                                                                                                                                              | HSKDA27                                                                                                                                                                                                                                                                                                                                                                    | HSKGN81              |
|                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                            | 207                  |

| 51:<br>45:                                                                                                                                 | .41:<br>23:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| .0438: 5, L0439: 5, L0751:<br>7, H0266: 4, L0665: 4,<br>.0777: 4, H0161: 3, H0645:<br>1, H0599: 3, H0594: 3,<br>.0763: 3, H0436: 3, L0747: | 1, L0758; 3, L0759; 3, L0759; 3, H0421; 3, H0426; 2, H0141; 2, S0045; 2, R0471; 2, T0641; 2, L0657; 2, L0657; 2, L0657; 2, L0664; 2, H0670; 2, L0664; 2, H0670; 2, L0664; 2, H0670; 2, L0664; 2, R0674; 2, L0749; 2, L0749; 2, L0749; 2, L0749; 2, L0749; 3, L07 | , 10757; L. 10585; L. 10586; S. 10589; S. 10589; S. 10672; L. 13643; L. 10740; L. 140715; L. 10740; L. 140254; L. 10926; L. 140402; S. 50360; L. 140619; L. 50498; L. 140619; L. 160459; L. | , H0614: 1, H0392: 1, 100455: 1, H0613: 1, H0592: 1, H0580: 1, H0580: 1, H0497: 1, H0492: 1, H0492: 1, H0492: 1, H0492: 1, H0492: 1, H04903: 1, H0492: 1, H04903: 1, H0492: 1, H04903: 1, H0492: 1, | L. LUOSS. 1, HU226.;<br>LO483. 1, H0286. 1, H0328.<br>LO483. 1, L0053. 1,<br>R0628. 1, H0169. 1, H0674.<br>S0366. 1, H0169. 1, H0674.<br>LH0268. 1, H0100. 1,<br>H0268. 1, H0100. 1,<br>H0421. 1, H0494. 1, S0014. |
|                                                                                                                                            | Arg-215 to Cliu-221, \$3 Thr-237 to Pro-242. B1 B1 Clium                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| Ceu-l<br>Glu-l<br>Phe-l<br>Pro-l<br>Glu-l                                                                                                  | Arg-2<br>Thr-2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| 0637:<br>7768:<br>0558:<br>7754: 1,<br>7754: 1,<br>7194: 1,<br>0506: 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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          |           |
| (1904): 1, 50002; 1, L0637; 1, L0646; 1, L0646; 1, L0734; 1, L0646; 1, L0734; 1, L0734                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                  | 1,0768, 1,1048; 3, 1,048; 3, 1,048; 3, 1,048; 3, 1,048; 3, 1,073; 3, 1,048; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 3, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4, 1,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073; 4,073                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           |
| 106411, \$0002.1,1<br>1.2051, 1.00461<br>1.00521, 1.00761<br>1.00521, 1.00761<br>1.00591, 1.00761<br>1.00781, 1.00531,<br>1.00781, 1.00531,<br>1.00781, 1.00531,<br>1.00481, 1.10672,<br>1.00781, 1.00781,<br>1.00781, 1.00781,<br>1.00781,<br>1.00781,<br>1.00781,<br>1.00781,<br>1.00781,<br>1.00781,<br>1.00781,<br>1.00781,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                  | 10.076 8, 12.49; 51, 10.076 8, 12.49; 51, 10.071 8, 13.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.071 13, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.072 11, 10.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | H0163: 2  |
| H06-<br>1, E3-<br>1, E077<br>1, E077<br>1, H0<br>8012<br>8012<br>1, H075<br>1, SC<br>1, |                  | 4, SG<br>1007<br>1007<br>1007<br>11, SG<br>11, SG<br>11, SG<br>11, SG<br>11, LC<br>11, SG<br>11, SG<br>11 | Н0        |
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|                                        |           |                                     |          |                            |                        |                            |                       |                            |                     |                            |                          |           |                   |                   |                  |                      |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
|                                        |           |                                     |          |                            |                        |                            |                       |                            |                     |                            |                          |           |                   |                   |                  |                      |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| H0163:1                                |           | S0007: 1, H0555: 1 and<br>.0026: 1. | S0022: 4 | L0766: 5, L0749: 3, S0134: | 2, L0770: 2, L0794: 2, | .0809: 2, L0790: 2, H0556: | , H0735: 1, L0622: 1, | I0457: 1, H0561: 1, L0662: | L0804: 1, L5622: 1. | 10436: 1, L0779: 1, L0731: | , L0758: 1, H0136: 1 and | 10506: 1. | H0309: 1          |                   |                  | .0439: 15, L0752: 6. | 0758-6 I 0438-5 I 0731- | L0803: 4. H0171: 3. | .0717: 3. H0251: 3. L0142: | 036-3 \$0422-3 1 0764- | 10659: 3 10666: 3 | 0664-3 \$0380-3 1.0754- | 10759: 3, 10591: 3 | 0608: 3 H0624: 2 T0002: | H0486: 2. H0052: 2. | 0471: 2, H0375: 2, S0002: | L0771: 2. L0766: 2. | 0776: 2, L0657: 2, L0517: | I 0665: 2 S0330: 2 S0028: | 1 0747: 2 1 0749: 2 | 0750-2 H0445-2 L0603- | 0. 2, 110445. 2, LOUGS. | 0786. 1 H0241. 1 C0308. | 50313, 1, 50353, 1 | 10255; 1, S0418; 1, T0007; |
| IOH_                                   |           | S0007:<br>S0026: 1.                 | 800      | L07                        | 5<br>2                 | 2080                       | 1, H                  | H045                       | 0.1                 | H043                       | 2                        | H050      | H03               |                   |                  | F07                  | r 075                   | 2                   | 1.07                       | 5                      | 200               | 1066                    | 100                | 1090                    | 2. HC               | 1047                      | 2. LO               | 1.077                     | 2                         | 1                   | 1,5                   |                         | 7, 11                   | 2                  | H025                       |
| Glu-23 to Asn-31,<br>Thr-38 to Gly-48. |           | Ser-6 to Arg-15.                    |          | Asp-23 to Gly-29.          |                        |                            |                       |                            |                     |                            |                          |           | Asp-26 to Asn-31, | Ser-37 to His-49, | Ala-65 to Ser-73 |                      |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| 614                                    | 177       | 615                                 | 919      | 617                        |                        |                            |                       |                            |                     |                            |                          |           | 819               |                   |                  | 619                  |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| 225 - 389                              | 232 - 309 | 96 - 332                            | 82 - 207 | 153 - 323                  |                        |                            |                       |                            |                     |                            |                          |           | 256 - 528         |                   |                  | 87 - 260             |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| 220                                    | 377       | 221                                 | 222      | 223                        |                        |                            |                       |                            |                     |                            |                          |           | 224               |                   |                  | 225                  |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| 1352201                                | 545060    | 460537                              | 892171   | 413246                     |                        |                            |                       |                            |                     |                            |                          |           | 596868            |                   |                  | 886200               |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| HSNMC45                                | HSNMC45   | 99d±ÖSH                             | HSRFZ57  | HSUBW09                    |                        |                            |                       |                            |                     |                            |                          |           | HSVBU91           |                   |                  | HSXGI47              |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |
| 210                                    |           | 211                                 | 212      | 213                        |                        |                            |                       |                            |                     |                            |                          |           | 214               |                   |                  | 215                  |                         |                     |                            |                        |                   |                         |                    |                         |                     |                           |                     |                           |                           |                     |                       |                         |                         |                    |                            |

| 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1                                                                                                                                              | 6: 18,<br>8. L0750:<br>6, L0395:<br>11: 5,<br>4, S0344:<br>1, L0599:                                                                                                                                  |
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| 1, 5938, 1, 59360, 1, 1, 5938, 1, 59360, 1, 1, 5904, 1, 5904, 1, 5904, 1, 5904, 1, 5904, 1, 5904, 1, 5904, 1, 5904, 1, 1, 5904, 1, 1, 1, 5904, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, | H0521: 40, H0046: 18,<br>10522: 11, L0747: 8, L0750:<br>8, S0002: 7, L0499: 7,<br>L0734: 7, H0486: 6, L0595:<br>6, H0556: 5, H0551: 5,<br>H0024: 4, H0622: 4, S0344:<br>4, H0519: 4, L0759: 4, L0599: |
|                                                                                                                                                                                       | Glin-14 to Thr-21, Arg-26 to Pro-31, Leu-43 to Pro-50, Leu-81 to Asp-88, Pro-153 to Thr-158, Pro-154 to Thr-222, Asp-228 to Asr-233, Pro-773 to Glin-282.                                             |
|                                                                                                                                                                                       | 620<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1<br>1                                                                                                    |
|                                                                                                                                                                                       | 448 - 1749                                                                                                                                                                                            |
|                                                                                                                                                                                       | 226                                                                                                                                                                                                   |
|                                                                                                                                                                                       | 1177537                                                                                                                                                                                               |
|                                                                                                                                                                                       | HSYAZ63                                                                                                                                                                                               |
|                                                                                                                                                                                       | 216                                                                                                                                                                                                   |

| 3:3,<br>3, L0369:<br>5:2,<br>1, S0046: 2,<br>2, L0021:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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|                                            | ),<br>0758:                                                                 | 0658:                                          | 0774:                     | 0547                  |                     | .2590                     |                       |                                                       | 0163:                      |                       | .992                      |                       | :670:                      | 3014                                       |                       | 0543:                      |                       | 0583:                      |                      | 0418:                      | 9                     | 378:                       | 0.400               | 0486:                      | .1000                 | .Tono              | 0328:                      |                       | 0413:                                           |
|                                            | H0618: 12, L0743: 10,<br>0794: 9, L0803: 9, L0758:<br>, L0731: 8, L0748: 7, | 0754: 6, H0545: 5, H0658:<br>H0052: 4 H0546: 4 | 0648: 4, L0662: 4, L0774: | , L0665: 4, L0779: 4, | H0521: 3, L0751: 3, | 0747: 3, H0295: 2, H0657: | , H0306: 2, S0420: 2, | . H0550: 2, S0360: 2, H0549:<br>. H0550: 2. H0253: 2. | 10544: 2, H0424: 2, H0163: | , H0551: 2, S0142: 2, | 0770: 2, L0769: 2, L0766: | , L0804: 2, L0806: 2, | 10700: 2, LU609: 2, L3023: | 0690 2, E0003: 2,<br>10690 2 H0672 2 S3014 | . S0027; 2, L0759; 2. | 10707: 2, S0192: 2, H0543: | , L3643: 1, H0686: 1, | ,0040: 1, H0294: 1, H0583: | 0254: 1,             | 10662: 1, H0402: 1, S0418: | , H0208: 1, S0045: 1, | 10393: 1, L3466: 1, S0278: | 3222: 1,            | 1058/: 1, HU333: 1, HU486: | , H0069; 1, S0049; 1, | H0620: 1, H0024: 1 | 70010: 1. H0286: 1. H0328: | , H0553: 1, H0628: 1, | 10617: 1, H0616: 1, H0413:<br>H0100: 1 H0646: 1 |
|                                            | 8: 12, L<br>9, L08(<br>11: 8, L(                                            | 6, H05                                         | 4, L06                    | 3.4, LO               | 21: 3, L            | 3, H02                    | )6: 2, SI             | 2, SU36<br>50: 2. H                                   | 2, H04                     | 51: 2, St             | 2, L07                    | 2; 2, E               | 2, LUS                     | 2.4.D                                      | 7: 2. LC              | 2, S01                     | B: 1, H               | 1, H02                     | , S0212: 1, H0254: 1 | 1, H04                     | 98: 1, S              | 1, L34                     | H0261: 1, S0222: 1, | , HO                       | 1, 20                 | , i                | 1. H02                     | 53: 1, H              | 1, H06                                          |
|                                            | H0618<br>L0794:<br>9, L073                                                  | L0754:                                         | L0648:                    | 4, L066<br>H0135      | 3, H05              | L0747:                    | 2, H030               | S0356:<br>2. H05                                      | H0544                      | 2, H05                | L0770:                    | 2, L080               | LUGUS                      | 2, LO                                      | 2. S002               | H0707                      | 2, L364               | S0040:                     | 1, S021              | H0662                      | 1, H020               | H0393                      | 1, H02              | / SCUT                     | 1, 1100               | H067               | T0010                      | 1, H05                | H0617:                                          |
| 78,<br>97.                                 |                                                                             |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
| o Asn-2<br>to Gly-2                        |                                                                             |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
| Thr-271 to Asn-278,<br>Glu-285 to Gly-297. |                                                                             |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | 622                                                                         |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | 150                                                                         |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | 59 - 1150                                                                   |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | 228                                                                         |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | 844835                                                                      |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | HTADW91                                                                     |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |
|                                            | 218                                                                         |                                                |                           |                       |                     |                           |                       |                                                       |                            |                       |                           |                       |                            |                                            |                       |                            |                       |                            |                      |                            |                       |                            |                     |                            |                       |                    |                            |                       |                                                 |

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| 80344.1, S0002.1,L0763.1,<br>L0637.1,L0394.1,L0763.1,<br>L0643.1,L0644.1,L0764.1,<br>L0737.1,L068.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0768.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L0769.1,L07 | H0250: 3, H0069: 2, L0771: 3, 2044: 2, H0050: 1, 10656: 1, H0486: 1, H0031: 3, 104013: 1, H0486: 1, L0768: 1, L0768: 1, L0789: 1, L0894: 1, L0658: 1, L0894: 1, L0658: 1, L0668: |           |           | HURSTI, 4, LOGGS, 3, 8033G. 10627. 2, LOGGS, 1, HODZS, 1, HODZS, 1, HODZS, 1, HODZS, 1, HOZGS, 1, HOZGS, 1, LOGGS, 1 |
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                                                                                                       |           |           | H0551: 4, L 2, S0360: 2, 1 L0527: 2, L0 2, H0333: 1, H0688: 1, H0 L0650: 1, L0 1, H0520: 1, H0682: 1, L0 and L0755: 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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                                                        | Pro-255 to Leu-264.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |           |           | Pro-22 to Glu-33.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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737 | 124 - 771 | 38 - 301                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| H0617: 10, S0410: 8,<br>0758: 8, L0769: 7, H0038: | , L0439: 6, L0750: 6, | .0752: 6, S0360: 5, L0775: | 0157: 4. H0620: 4. H0087: | , S0440: 4, S0344: 4, L0763: | , S0328: 4, L0747: 4, | I0224: 3, H0484: 3, H0402: | , S0049; 3, H0708; 3, | .0773: 3, L0805: 3, L0809: | , L0519; 3, H0670; 3, | 0748: 3, L0731: 3, L0757: | , L0581: 3, H0295: 2, | 10341: 2, S0444: 2, S0222: | , L0622: 2, H0253: 2, | (0309: 2, T0115: 2, H0544: | H0545: 2, H0081: 2, | 10012: 2, H0673: 2, S0036: | H0616: 2, L0770: 2, | 0774: 2, L0518: 2, H0725: | , S0374: 2, H0696: 2, | 0588: 2, H0543: 2, L0615: | , H0160: 1, H0225: 1, | 10713: 1, S6024: 1, S0430: | , H0656: 1, S0116: 1, | .0212: 1, H0483: 1, H0306: | , H0638: 1, H0125: 1, | 0420: 1, S0358: 1, S0408: 1, | I0637: 1, S0476: 1, H0640: | , H0411: 1, S0278: 1, | 10441: 1, H0461: 1, H0298: | , H0333: 1, L0623: 1, | 10486: 1, H0427: 1, H0156: | , H0599: 1, T0082: 1, | '0048: 1, H0318: 1, H0581: | , H0196: 1, H0597: 1, | .0738: 1, H0530: 1, H0242:<br>H0024: 1 H0373: 1 |
| H [0]                                             | 6,1                   | 5;                         | 3.5                       | 4,<br>S                      | 4, S                  | HO                         | 3,8                   | 202                        | 3,1                   | 5                         | 3,1                   | H0.                        | 2,1                   | HO                         | 7,1                 | HO                         | 7,                  | E01                       | 2,8                   | 2                         | 1, E                  | HO                         | 1, E                  | S02                        | 1, F                  | S04                          | Ĕ                          | 1, E                  | ΞÓ                         | 1, E                  | 7OH                        | 1,1                   | 10<br>10                   | Τ,                    | 9 -                                             |
| Gly-41 to Leu-46,<br>Asp-67 to Thr-75,            | Ilc-114 to Gly-122,   | Pro-156 to Trp-161.        |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |
| 625                                               |                       |                            |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |
| 13 - 546                                          |                       |                            |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |
| 231                                               |                       |                            |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |
| 1352365                                           |                       |                            |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |
| HTECC05                                           |                       |                            |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |
| 221                                               |                       |                            |                           |                              |                       |                            |                       |                            |                       |                           |                       |                            |                       |                            |                     |                            |                     |                           |                       |                           |                       |                            |                       |                            |                       |                              |                            |                       |                            |                       |                            |                       |                            |                       |                                                 |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Gly-41 to Leu-46,<br>Asp-67 to Thr-75,<br>Ile-114 to Pro-127. | Gly-41 to Leu-46,<br>Asp-67 to Thr-75,<br>Ile-114 to Ala-123. | Met-1 to His-7.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HTECC05                                                       | HTECC05                                                       | HTEEB42                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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|                                                 | 38:                                                                                                                                                                                       |                        | 54:<br>59:<br>77:                                                                                                                                                            |                                                                                    |           | 331;<br>41;<br>56:<br>77;                                                                                                                                                                                                                                          |                                  |                   |                                                             |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------|-------------------------------------------------------------|
| , L0749: 1, L0777: 1,<br>.0780: 1 and L0599: 1. | H0486: 3, H0253: 1, H0544:<br>H0012: 1, 80388: 1,<br>H053: 1, H0090: 1, H0038:<br>1, H0652: 1, L0769: 1,<br>L0641: 1, L0806: 1, H0696:<br>1, L0748: 1, L0749: 1,<br>5003: 1 and S0196: 1. | H0038: 1 and L0758: 1. | L0758: 4, L0770; 2, L0754;<br>, L0779; 2, L3643; 1,<br>, L0764; 1, L0798; 1, L0769;<br>, L0764; 1, L0794; 1,<br>, L0788; 1, L0777;<br>, L0780; 1, L0731; 1 and<br>, 0465; 1, |                                                                                    |           | L0788-3, Sq4082, 1,10031. , H00321: 2, L0782, 2, L0782, 2, L0782, 2, L0782, 1, L0782, 1, L0782, 1, L0111: 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 17001: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, | H0616: 2, L0758: 2 and 10038: 1. | H0253: 1          | S0114: 1 and H0264: 1.                                      |
| 1                                               | Gly-35 to Gly-40.                                                                                                                                                                         |                        | Tyr-37 to Cys-49,<br>Gly-51 to Tyr-56,<br>Lys-88 to Trp-93,<br>Prb-125 to Lys-140,<br>Lys-147 to Thr-153,<br>Thr-175 to Asn-188,<br>Ala-203 to Met-208.                      | Tyr-37 to Cys-49,<br>Gly-51 to Tyr-56,<br>Lys-88 to Trp-93,<br>Lcu-130 to Glu-136. |           |                                                                                                                                                                                                                                                                    | Pro-98 to Gln-106.               | Ser-33 to Lys-43. | Pro-22 to Pro-28,<br>Pro-41 to His-48,<br>Pro-79 to His-86, |
|                                                 | 627                                                                                                                                                                                       | 628                    | 629                                                                                                                                                                          | 778                                                                                | 622       | 630                                                                                                                                                                                                                                                                | 169                              | 632               | 633                                                         |
|                                                 | 231 - 371                                                                                                                                                                                 | 90 - 284               | 156 - 779                                                                                                                                                                    | 163 - 639                                                                          | 155 - 367 | 164 - 298                                                                                                                                                                                                                                                          | 15 - 491                         | 73 - 378          | 91 - 783                                                    |
|                                                 | 233                                                                                                                                                                                       | 234                    | 235                                                                                                                                                                          | 384                                                                                | 385       | 236                                                                                                                                                                                                                                                                | 237                              | 238               | 239                                                         |
|                                                 | 543396                                                                                                                                                                                    | 381995                 | 1352272                                                                                                                                                                      | 658744                                                                             | 381941    | 836072                                                                                                                                                                                                                                                             | 847090                           | 634852            | 665745                                                      |
|                                                 | HTBFU65                                                                                                                                                                                   | HTEGA76                | HEJN13                                                                                                                                                                       | HTEIN13                                                                            | HTEJN13   | НТБ.Р.I.7                                                                                                                                                                                                                                                          | HTELS08                          | HTLEP53           | HTOIY21                                                     |
|                                                 | 223                                                                                                                                                                                       | 224                    | 225                                                                                                                                                                          |                                                                                    |           | 226                                                                                                                                                                                                                                                                | 227                              | 228               | 229                                                         |

| 10438, 6, L0439, 5, H0661; 1 1, L0776; 3, H0556; 2 10100; 2, L0598; 2, L0764; 1 1, L0776; 3, H0556; 2 10775; 1, H0556; 1 10740; 1, H0719; 1, H0759; 1 10140; 1, 1, H0719; 1 10140; 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | nd H0422: 1. | H0622: 7, 80360: 3, L0809: X<br>, L0804: 2, L0774: 2,<br>.0775: 2, L0748: 2, H0484:<br>, H0014: 1, S0440: 1, |
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| (3he-134, 3he-134, 3h | and HO       | Ser-29 to Ser-34, H062<br>Ser-186 to Asp-196, 3, L086<br>Arg-206 to Ser-225. L0775:                          |
| 460                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 780          |                                                                                                              |
| 2365 - 2577                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 530 - 745    | 118-810                                                                                                      |
| 240                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 386          | 241                                                                                                          |
| 854941                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 56683        | 916616                                                                                                       |
| HTPCS72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HTPCS72      | нтрін83                                                                                                      |
| 230                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |              | 231                                                                                                          |

|                                                                                                 |                   |          |                            |                                                                             | Т                          |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | T                | Т                | Т                 | T                 |                       |                            |                       |                        |
|-------------------------------------------------------------------------------------------------|-------------------|----------|----------------------------|-----------------------------------------------------------------------------|----------------------------|------------------------------|------------------------|----------------------------|-----------------------|---------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|---------------------|----------------------------|-----------------------|------------------|------------------|-------------------|-------------------|-----------------------|----------------------------|-----------------------|------------------------|
|                                                                                                 |                   |          |                            |                                                                             |                            |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       |                  |                  |                   |                   |                       |                            |                       |                        |
|                                                                                                 |                   |          |                            |                                                                             |                            |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       |                  |                  |                   |                   |                       |                            |                       |                        |
| J. L0646: 1, L0643: 1, L0374: 1, L0764: 1, L0771: 1, L0773: 1, L0662: 1, L0803: 1 and L0788: 1. |                   |          | H0087: 1, S0002: 1, L0769: | 10670: 1, 10683: 1,<br>10670: 1, L0748: 1, L0749:<br>10757: 1 and 1 0758: 1 | L0803: 4, L0731: 4, L0774: | , S0380: 3, S0028: 3, L0758: | i, H0486: 2, S0003: 2, | 10040: 2, S0344: 2, L0766: | 0748-2 L0756-2 L0777- | L0780; 2, L0753; 2, | 0011: 2, H0716: 1, H0638: | , L0617: 1, S0358: 1, | 10411: 1, S0280: 1, H0318: | , H0355: 1, H0674: 1, | H0212: 1, H0135: 1, H0038: | , H0132: 1, S0142: 1, | 0002: 1, H0529: 1, L0804: | , L0632: 1, L0666: 1, | 10682: 1, H0684: 1, H0525: | S0044: 1, S0406: 1, | 10555: 1, L0747: 1, L0750: | , L0752: 1, L0755: 1, | H0040-1          |                  |                   |                   | L0803: 10, L0748: 10, | .0439; 8, L0438; 7, L0752; | 0603.7 H0661.6 L0740. | 5, L0779: 5, L2654: 4, |
|                                                                                                 | Ser-29 to Ser-34. |          |                            | - 12                                                                        | Glu-55 to Arg-61,          | 63                           | Ser-99 to Ser-104.     | = 0                        | *L ==                 | 1.61                | 8                         | 1                     | <u> </u>                   | _                     |                            | -                     | 20.                       |                       | 4                          | -                   | -                          |                       | Len-37 to Asn-42 | Len-37 to Asn-42 | I ve 41 to Ann 46 | Lys-41 to Atg-40. |                       |                            | <u> </u>              | 2                      |
|                                                                                                 | 781               | 782      | 969                        |                                                                             | 637                        |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | 889              | 783              | 78.4              | +0/               | 639                   |                            |                       |                        |
|                                                                                                 | 111 - 530         | 96 - 353 | 170 - 283                  |                                                                             | 133 - 534                  |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | 05 - 223         | 100 - 228        | 175 400           | 704-011           | 185 - 319             |                            |                       |                        |
|                                                                                                 | 387               | 388      | 242                        |                                                                             | 243                        |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | 244              | 380              | 300               | 330               | 245                   |                            |                       |                        |
|                                                                                                 | 895024            | 880868   | 460579                     |                                                                             | 637725                     |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | 1008159          | 863187           | 75/1/25           | 071407            | 634083                |                            |                       |                        |
|                                                                                                 | HTPIH83           | HTPIH83  | HTSEW17                    |                                                                             | HTTBI76                    |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | HTTRS64          | HTTBS64          | LASGTTI           | H11D30+           | HTWKE60               |                            |                       |                        |
|                                                                                                 |                   |          | 232                        |                                                                             | 233                        |                              |                        |                            |                       |                     |                           |                       |                            |                       |                            |                       |                           |                       |                            |                     |                            |                       | 234              |                  |                   |                   | 235                   |                            |                       |                        |

| .0747: 4, L0759: 4, L0596: | , H0556: 3, S0010: 3, | 10031: 3, H0644: 3, L0766: | , L0774: 3, L0749: 3, | 0758: 3, L0591: 3, L0608: | . S0011: 3, H0657: 2, | .0549; 2, L3816; 2, H0486; | , L0471: 2, S6028: 2, | 0455: 2. H0529: 2. L0794: | 10775: 2 10517: 2 | (2) 2) TOE 10: 2, | 0665: 2, H0519: 2, L0602: | S0028: 2, L0754: 2, | 0755: 2, H0667: 2, H0542: | . H0422: 2, H0265: 1. | 0220: 1, S0134: 1, H0656: | T 2905 - 1 H0402 - 1 | 0420.1 C0259.1 H0590. | 2021, 30338: 1, H0380: | H0735: 1, H0747: 1, | 0645: 1, H0619: 1, H0393: | . L2814: 1, H0437: 1, | 6022: 1. H0431: 1. H0586: | L3817: 1. H0643: 1. | 0156: 1. H0004: 1. H0581: | H0052; 1, H0263; 1, | 0596; 1, T0110; 1, H0024; | H0014: 1, H0266: 1, | 00003: 1, H0615: 1, H0070: | H0030: 1, H0628: 1, | 10032: 1, H0598: 1, H0591: | H0038: 1, H0264: 1, | 10494: 1, S0440: 1, L0773: | , L0662: 1, L0363: 1, | 0804: 1, L0650: 1, L0375: | L0805: 1. L0776: 1. | 0655; 1, L0658; 1, L0783; | . L0809; 1. L5622; 1. | 0791: 1, L0666: 1, S0053: | , L2257: 1, L2258: 1, | S0374: 1, L3826: 1, H0520: |
|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-------------------|-------------------|---------------------------|---------------------|---------------------------|-----------------------|---------------------------|----------------------|-----------------------|------------------------|---------------------|---------------------------|-----------------------|---------------------------|---------------------|---------------------------|---------------------|---------------------------|---------------------|----------------------------|---------------------|----------------------------|---------------------|----------------------------|-----------------------|---------------------------|---------------------|---------------------------|-----------------------|---------------------------|-----------------------|----------------------------|
| 100                        | 4, H                  | 00H                        | 3, L                  | L07                       | 3,8                   | HOS                        | 7,7                   | 107                       | - 6               | 1,5               | 907                       | 13.8                | E07                       | 2. ⊞                  | HOZ                       |                      | 200                   | #06<br>#1              | H,H                 | 90H                       | 1.1                   | Se0                       | 1.1                 | IOH<br>I                  | 1.1                 | HOS                       | 1, H                | 008                        | H,1                 | 00H                        | 1, H                | HOH                        | 1, L                  | 108                       | 1.1                 | 907                       | 1.1                   | 100                       | 1,1                   | 803                        |
|                            |                       |                            |                       |                           |                       |                            |                       |                           |                   |                   |                           |                     |                           |                       |                           |                      |                       |                        |                     |                           |                       |                           |                     |                           |                     |                           |                     |                            |                     |                            |                     |                            |                       |                           |                     |                           |                       |                           |                       |                            |
|                            |                       |                            |                       |                           |                       |                            |                       |                           |                   | _                 | _                         | _                   |                           |                       |                           | _                    |                       |                        | _                   |                           |                       |                           |                     |                           |                     |                           |                     |                            |                     |                            |                     |                            |                       |                           |                     |                           |                       |                           |                       |                            |
|                            |                       |                            |                       |                           |                       |                            |                       |                           |                   |                   |                           |                     |                           |                       |                           |                      |                       |                        |                     |                           |                       |                           |                     |                           |                     |                           |                     |                            |                     |                            |                     |                            |                       |                           |                     |                           |                       |                           |                       |                            |

| I, S0126: I, H0658: I, H0660: I, H0621: I, H0521: I, H0521: I, L0731: I, S0031: I, S0031: I, S0031: I, L0731: I, L0380: I, L0380: I, L0380: I, L0378: I and L3631: I, L0378: I, L0378: I and L3631: I, L0378: I, L03 | H0265: 1 and H0264: 1. | L0766; 5, H0313; 3, H0624;<br>L1, H0555; 1, H0529; 1, H0486;<br>L1, H0156; 1, H02399; 1, H0409; 1, H0409; 1, H0109;<br>L1, S0250; 1, H0109;<br>L2, L0793; 1, L0752; 1, L0799; 1, L0793; 1, L | 1,0755.5, 10.699.4, 10.0755.5, 10.699.4, 10.0755.5, 10.699.4, 10.0755.5, 10.059.2, 10.059.2, 10.0755.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0759.2, 10.0775.2, 10.0994.1, 10.0775.2, 10.0966.2, 10.0775.2, 10.0966.2, 10.0775.2, 10.0966.2, 10.0775.2, 10.0966.2, 10.0775.2, 10.0966.2, 10.0775.2, 10.0966.2, 10.0775.2, 10.0775.2, 10.0966.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.0775.2, 10.075.2, 10.075.2, 10.075.2, 10.075.2, 10.075.2, 10.075.2, 10.075.2, 10.075.2, 10.075.2, 10.0 |
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                                               | Lys-99 to Arg-107.     | Lys-yu o Arg-107.<br>Asp-51 to His-56.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Met-I to Pro-6,<br>Gly-73 to Thr-78.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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426               | 91 - 426<br>328 - 498                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 421 - 657                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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                                               | 1310814                | 55/434<br>603918                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| 1, L0599: 1, L0603: 1,<br>H0543: 1, H0422: 1 and<br>H0506: 1. |                                      | 5:1                      | L0777: 7, L0751: 3, L0766: | , L0438: 2, L0779: 2, | 2, H0351: 1, S0222: | , H0333: 1, H068/: 1, | 10646: 1, L0770: 1, L0642: | , L0662: 1, L0803: 1, | .0375: 1, L0805: 1, L0653: | , L0659: 1, L0790: 1, | .0663: 1. L0664: 1. L0665: 1 | nd H0506; 1. | H0171: 3, L0754: 3, H0431: | . H0196: 2. H0546: 2. | 10623; 2, H0539; 2, H0696; | , L0744; 2, L0748; 2, | .0749: 2, L0758: 2, L0759: | 8: 2, H0624: 1, | .0002: 1, S0040: 1, H0341: | , S0360: 1, H0580: 1, | 10587: 1, H0574: 1, H0486: | , H0036: 1, S0665: 1, | 0123: 1, H0014: 1, S6028: | , S0214: 1, H0553: 1, | I0032: 1, L0455: 1, H0598: | , H0038: 1, H0616: 1, | 10056: 1, S0386: 1, S0112: | . T0042: 1, S0344: 1, S0422: | S0002: 1, L0775: 1. | 0806: 1, 1,0805: 1, 1,0776: | S0152-1 H0704-1 | 10555; 1, H0436; 1, L0439; | , L0751: 1, L0752: 1, | .0731: 1, L0588: 1, L0592: |
|---------------------------------------------------------------|--------------------------------------|--------------------------|----------------------------|-----------------------|---------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------------|------------------------------|--------------|----------------------------|-----------------------|----------------------------|-----------------------|----------------------------|-----------------|----------------------------|-----------------------|----------------------------|-----------------------|---------------------------|-----------------------|----------------------------|-----------------------|----------------------------|------------------------------|---------------------|-----------------------------|-----------------|----------------------------|-----------------------|----------------------------|
| 1, L0599<br>H0543: 1<br>H0506: 1                              | Met-1 to Pro-6,<br>Gly-73 to Thr-78. | Ala-45 to Gly-50. H0556: | Pro-31 to Ala-37. L0777    | 2, L043               | 110352              | 1, H03.               | H0646                      | 1, L06e               | L0375:                     | 1, L06                | F0963                        | and H0       | H017                       | 2. HOI                | H0623                      | 2, L074               | L0749:                     | 2, S039         | T0002:                     | 1, S036               | H0587;                     | 1, H00                | H0123:                    | 1, S021               | H0032                      | 1, H00:               | H0056                      | 1. T004                      | 0005                | 1.0806                      | 5108 1          | H0555                      | 1, L07                | L0731:                     |
|                                                               | N 987                                | 643 A                    | 644 P                      |                       |                     |                       |                            |                       |                            |                       |                              |              | 645                        | :                     |                            |                       |                            |                 |                            |                       |                            |                       |                           |                       |                            |                       |                            |                              |                     |                             |                 |                            |                       |                            |
|                                                               | 330 - 566                            | 72 - 230                 | 123 - 275                  |                       |                     |                       |                            |                       |                            |                       |                              |              | 14-151                     |                       |                            |                       |                            |                 |                            |                       |                            |                       |                           |                       |                            |                       |                            |                              |                     |                             |                 |                            |                       |                            |
|                                                               | 392                                  | 249                      | 250                        |                       |                     |                       |                            |                       |                            |                       |                              |              | 251                        | i                     |                            |                       |                            |                 |                            |                       |                            |                       |                           |                       |                            |                       |                            |                              |                     |                             |                 |                            |                       |                            |
|                                                               | 834438                               | 838288                   | 638402                     |                       |                     |                       |                            |                       |                            |                       |                              |              | 571200                     |                       |                            |                       |                            |                 |                            |                       |                            |                       |                           |                       |                            |                       |                            |                              |                     |                             |                 |                            |                       |                            |
|                                                               | S64XXIH                              | HTXON32                  | HUFCJ30                    |                       |                     |                       |                            |                       |                            |                       |                              |              | HI IVER53                  |                       |                            |                       |                            |                 |                            |                       |                            |                       |                           |                       |                            |                       |                            |                              |                     |                             |                 |                            |                       |                            |
|                                                               |                                      | 239                      | 240                        |                       |                     |                       |                            |                       |                            |                       |                              |              | 241                        |                       |                            |                       |                            |                 |                            |                       |                            |                       |                           |                       |                            |                       |                            |                              |                     |                             |                 |                            |                       |                            |

| p                                      | _                                   |           |         |           |                       |                                        |                   | 365:                       |                        | 318:                       |                        | :66:                       |                        | 334:                       |                        | :04                        |                        | :45:                       |                        | :819:                      |                        | :06:                      |                        | 70:                       |                        | 42:                        |                        | 58:                        |                        | 81:                        |                        | 134:                       |                        | 45:                        |
|----------------------------------------|-------------------------------------|-----------|---------|-----------|-----------------------|----------------------------------------|-------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|---------------------------|------------------------|---------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|------------------------|----------------------------|
| 1, S0026: 1, H0543: 1 and<br>H0423: 1. | H0441: 1, H0581: 1 and<br>H0604: 1. |           |         | H0581: 1  | H0580: 1 and H0169: 1 |                                        |                   | H0556: 7, H0581: 5, H0265: | 4, H0083: 4, H0424: 4, | H0543: 4, H0580: 3, H0318: | 3, L0766: 3, L0783: 3, | H0422: 3, H0650: 2, L2599: | 2, H0069: 2, H0635: 2, | H0457: 2, H0620: 2, H0634: | 2, L3144: 2, L0764: 2, | L0666: 2, L0758: 2, H0740: | 1, H0656: 1, H0341: 1, | L3684: 1, H0637: 1, H0645: | 1, H0393: 1, L3312: 1, | H0610: 1, H0333: 1, H0618: | 1, H0309: 1, H0009: 1, | H0050: 1, H0051: 1, H0290 | 1, H0617: 1, S0038: 1, | S0426: 1, H0529: 1, L0770 | 1, L0761: 1, L0667: 1, | L0772: 1, L0646: 1, L0642. | 1, L0643: 1, L0773: 1, | L0774: 1, L0655: 1, L0558. | 1, L0665: 1, H0701: 1, | L2467: 1, L0438: 1, L2681: | 1, H0520: 1, H0670: 1, | H0521: 1, H0522: 1, H0134: | 1, L0748: 1, L0439: 1, | L0/51: 1, L0/56: 1, H0445: |
|                                        | Pro-53 to Trp-61.                   |           |         |           | Trp-47 to Thr-54,     | Ser-68 to Asn-73,<br>Ser-86 to Gly-92. | Trp-47 to Thr-54. | Ser-165 to His-174,        | Met-196 to Asp-204,    | Lys-212 to Leu-218,        | Pro-277 to Leu-285,    | Pro-290 to Arg-298,        | Ser-402 to Ser-407,    | Trp-465 to Gly-470,        | His-698 to His-706,    | Asp-793 to Asn-801,        | Gln-830 to Lys-838,    | Gly-862 to His-867,        | Ala-871 to His-877,    | Lys-1063 to Asn-1069,      | Ser-1100 to Ser-1108,  | Asn-1194 to Ser-1200,     | Leu-1308 to Gly-1314,  | Lys-1437 to Asn-1442,     | Asp-1583 to Val-1599,  | Thr-1651 to Lys-1656,      | Lys-1735 to Gly-1740,  | Arg-1789 to Tyr-1795,      | Arg-1846 to His-1854,  | Pro-1869 to Pro-1875.      |                        |                            |                        |                            |
|                                        | 646 I                               | 787       | 788     | 647       | 648                   | 0.0.                                   |                   |                            | ~                      |                            |                        |                            | 0,                     | -                          |                        |                            |                        |                            |                        | _                          | 0,                     |                           | _                      | _                         |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |
|                                        | 322 - 825                           | 322 - 483 | 312-818 | 581 - 709 | 243 - 560             |                                        | 233 - 550         | 75 - 5738                  |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                           |                        |                           |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |
|                                        | 252                                 | 393       | 394     | 253       | 254                   |                                        | 395               | 255                        |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                           |                        |                           |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |
|                                        | 838626                              | 833089    | 793875  | 905662    | 846382                |                                        | 646977            | 949402                     |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                           |                        |                           |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |
|                                        | HWAAD63                             | HWAAD63   | HWAAD63 | HWADJ89   | HWBCP79               |                                        | HWBCP79           | HWBEM18                    |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                           |                        |                           |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |
|                                        | 242                                 |           |         | 243       | 244                   |                                        |                   | 245                        |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                            |                        |                           |                        |                           |                        |                            |                        |                            |                        |                            |                        |                            |                        | 1                          |

| , S0436: 1 and H0216: 1. |           |          | 10.077: 4.10042: 3. 2.1077: 4.10042: 3. 2.1065: 2.10745: 3.10265: 3. 2.1065: 2.10745: 3.10265: 3. 2.1065: 2.10745: 3.10265: 3. 2.1065: 2.10745: 3.10745: 3. 2.10042: 3.10745: 3. 2.10042: 3.10745: 3. 2.10042: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.10745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3.20745: 3. 2.10745: 3. 2.10745: 3.20745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.10745: 3. 2.1 | S 8012:8, L. 222:8, H0564;<br>S 8012:8, L. 222:8, H0564;<br>S 90476:5, S 9030:5, L0755:5,<br>O751:4, L0581:4, L5623;<br>H0682:2, H0031:2,<br>H0696:2, L0776:2, L0899;<br>H0696:2, L0776:2, L0899; |
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|                          |           |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Lys-39 to Cys.4, Pro-87 to Gly-93, Glm-107 to Ala-115, Glu-130 to Val-138, Glu-149 to Ser-155, 3 Asu-163 to Tyr-169, Glu-217 to Ple-231,                                                          |
|                          | 790       | 16/      | 059                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 651                                                                                                                                                                                               |
|                          | 65 - 2725 | 1 - 1494 | 271 - 426                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 33 - 1073                                                                                                                                                                                         |
|                          | 396       | 397      | 256                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 257                                                                                                                                                                                               |
|                          | 906580    | 877573   | 799427                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 886212                                                                                                                                                                                            |
|                          | HWBEM18   | HWBEM18  | HWBFX31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HWHGZ51                                                                                                                                                                                           |
|                          |           |          | 246                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 247                                                                                                                                                                                               |

| 10486:<br>10486:<br>10181:<br>0783:<br>0752:<br>3:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | H0351:                                                                                                 | ,0010:<br>,0758:<br>,0051:<br>,0051:<br>,0064:<br>,0606:<br>,0547:<br>,0331:<br>,11.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | : 2.                                                                               |
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| 10556,1,10295-1,10177. 1,10658,1,10370-1, 1,10658,1,10370-1, 1,1058,1,1037-1,10486. 1,10571-1,10487-1,10489. 1,10571-1,10589-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,10789-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, 1,1057-1,1078-1, | L0439; 4, L0748; 2, H0351;<br>, S0364; 1, L0768; 1,<br>, L0650; 1, L0375; 1, L0747; 1<br>and H0352; 1. | 1,0742, 3, 1072, 3, 800, 1, 10742, 3, 1072, 3, 1072, 3, 1072, 3, 1072, 3, 1072, 3, 1072, 3, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1073, 2, 1 | H0415; 3 and H0414; 2.                                                             |
| 56: 1, H<br>92: 1, H<br>92: 1, H<br>2539: 1, 1<br>81: 1, H<br>0617: 1,<br>53: 1, L0<br>5622: 1, 1<br>50: 1, S0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | L0439: 4, L07<br>1, S0364: 1, LC<br>L0650: 1, L037<br>and H0352: 1.                                    | 754: 14, 174, 1754: 14, 1754: 14, 1754: 14, 1759: 2, 1759: 2, 1759: 2, 1759: 2, 1759: 2, 1759: 2, 1759: 2, 1759: 1, 116: 1, 116: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759: 1, 1759:  | 415: 3 аг                                                                          |
| HOS<br>HOS<br>HOS<br>HOS<br>HOS<br>HOS<br>HOS<br>HOS<br>HOS<br>HOS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1, S<br>200<br>and and                                                                                 | 100<br>100<br>100<br>100<br>100<br>100<br>100<br>100<br>100<br>100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | H.                                                                                 |
| 273,<br>-284,<br>-295,<br>-325.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 68,<br>90,<br>-110,                                                                                    | Ö.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 40,<br>58,<br>95,<br>-169,                                                         |
| Pro-265 to Pro-273,<br>Pro-275 to Val-284,<br>Ala-288 to Arg-295,<br>Gln-304 to Gly-325,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Tyr-59 to Gln-68,<br>His-84 to Leu-90,<br>Ser-105 to Asn-110,<br>Leu-112 to Pro-118.                   | Sqr-24 to Tm-30.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Thr-28 to Tyr-40,<br>Gln-61 to Ser-68,<br>Glu-74 to Lys-95,<br>Glu-163 to Thr-169, |
| Pro-2<br>Pro-2<br>Ala-2<br>Gln-3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Tyr-5<br>His-8<br>Ser-1<br>Leu-1                                                                       | Ser-2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Gh-6<br>Gh-7<br>Gh-1<br>Gh-1                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 652                                                                                                    | 653                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 654                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 909 - 601                                                                                              | 166 - 255                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 76 - 1167                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 139                                                                                                    | 991                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | - 92                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 258                                                                                                    | 259                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 260                                                                                |
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| Thr-28 to Tyr-40,<br>Gln-61 to Ser-68,<br>Glu-74 to Leu-94. | Thr-28 to Tyr-40,<br>Gln-61 to Ser-68. | Thr-28 to Tyr-40,<br>Gln-61 to Ser-68,<br>Gly 24 to I yr 05                                               | Thr-119 to Leu-124,<br>Pro-126 to Gln-131.                                                                                                                    |                                                                         |                                                                                                 |                                                                                                                           | Phe-8 to Ser-13,                                                                                                        | Val-81 to Arg-87,<br>Asp-98 to Pro-104.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Phe-8 to Ser-13,<br>Ala-84 to Ser-90                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 792                                                         | 793                                    | 794                                                                                                       |                                                                                                                                                               | 795                                                                     | 962                                                                                             | 797                                                                                                                       | 929                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 798                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 81 - 419                                                    | 81 - 419                               | 76 - 495                                                                                                  |                                                                                                                                                               | 23 - 46                                                                 | 158 - 202                                                                                       | 3 - 866                                                                                                                   | 58 - 423                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 66 - 359                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 398                                                         | 399                                    | 400                                                                                                       |                                                                                                                                                               | 401                                                                     | 402                                                                                             | 403                                                                                                                       | 197                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 404                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 967554                                                      | 069818                                 | 905734                                                                                                    |                                                                                                                                                               | 902326                                                                  | 885140                                                                                          | 618908                                                                                                                    | 1352287                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 704101                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| НОРОСЗЗ                                                     | НОРОСЗЗ                                | НОРОСЗЗ                                                                                                   |                                                                                                                                                               | HOFOC33                                                                 | HOFOC33                                                                                         | HOFOC33                                                                                                                   | HSDEZ20                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSDEZ20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                             |                                        |                                                                                                           |                                                                                                                                                               |                                                                         |                                                                                                 |                                                                                                                           | 251                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                             | 967554 398 81 - 419 792                | 967554         398         81 - 419         792           878690         399         81 - 419         793 | 967554         398         81-419         792           878690         399         81-419         793           905734         400         76-495         794 | 967554 398 81-419 792<br>878690 399 81-419 793<br>905734 400 76-495 794 | 967354 398 81-419 792<br>878690 399 81-419 793<br>905734 400 76-495 794<br>902326 401 23-46 795 | 967554 398 81-419 792<br>878600 399 81-419 793<br>905734 400 76-495 794<br>902326 401 23-46 795<br>885140 402 188-202 796 | 967554 398 81-419 792<br>878690 399 81-419 793<br>905734 400 76-495 794<br>902326 401 23-46 795<br>888519 402 3-866 797 | HOPCC33 867554 398 81-419 792 Thr-28 0 Ty-40, Thr-81 1 Thr-81 0 Ty-40, Thr-81 1 Thr-81 0 Ty-40, Thr-81 0 Ty-40 | HOPOC33 967554 398 81-419 792 Thr-28 0 Ty-40, Gib-61 to Ser-68 (Gib-61 to Ser-68)   HOPOC33 878690 399 81-419 793 Thr-28 to Ty-40, Gib-61 to Ser-68 (Gib-61 to Ser-68)   HOPOC33 902734 400 76-495 794 Thr-28 to Ty-40, Gib-61 to Ser-68 (Gib-61 to Ser-68)   HOPOC33 90225 401 23-46 795 Thr-119 to Leu-124, Thr- |

| ble 1B.2 | ble 1B.2    | Contia | OEO ID | Tissue Distribution Library Code-Count                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| No:      | m 2000 Crom | ë      | NO:X   | (see Table 4 for Library Codes)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| _        | HZCBU83     | 884134 | 11     | MRIRES, MARGS, ARROS, ARRISG, SARIGG, ARAZGG, ARAZGG, ARAZGS, ARRISG, ARRISG, ARRISG, ARRISG, ARRISG, ARRISG, ARRISG, ARRISG, ARROSG, ARRISG, ARRISG, ARROSG,  |
|          | H2CBU83     | 745366 | 259    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 2        | H6EDC19     | 543259 | 12     | MR22521, ARCHO, PARCESTI, ARCHOLI, ARGOBIL, ARITSO, ARCHO, PARCESO, ARCHOSO, ARCHO, AR |

|          |         |        |     | [H0672:1, H0539:1, S0146:1, L0751:1, L0780:1, L0731:1, S0434:1 and S0196:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>б</b> | НАСВЪЭ1 | 637482 | 13  | RROBSTIG, KARSBI GA, KAROBS-S, KARSS-S, KARSS-S, KARGOS-A, KRIGG-4, KAROS-30, RAZUG-4, KAROS-30, RAZUG-4, KAROS-10, KAROG-19, KAROT-19, KAZT-19, KAZD-11, KA |
| 4        | HACCII7 | 891114 | 14  | AR22115, AR2195, AR2738, AR2657, AR2246, AR215, AR2154, AR2195, AR27154, AR21554, AR3184, AR2664, AR2064, AR2062, AR2052, AR2052, AR2052, AR2062, AR2061, AR20 |
|          | HACCI17 | 731877 | 260 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 'n       | HAGAQ26 | 966195 | 15  | MR22429, ARIO-29, ARIO-28, ARIOFS, ARIONS, ARIONS, ARDON, ARIOTO, ARIO |

| HAGDESS   S45617   261 |
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| HAIFLIS 676933  HAJAN23 1352364  HAJAN23 872551  HAJBR69 638516 |            | 20 MR0523, ARR5929, ARR9427, ARS9426, AGR9217, ARS0216, ARS021, ARS0213, ARS221, ARS230, ARS1420, ARR9426, ARS1519, ARR9426, ARS1519, ARR9418, ARS0611, ARS1611, ARR9418, ARS0611, ARS0611, ARR9418, ARS0611, ARS0 | <ol> <li>ARRU27, ARRIPGA, ARZDYG, ARRIPGA, ARREAS, ARZD-44, ARZD24, ARRIPGA, ARREAS, ARREAS, ARRIPGA, ARREAS, ARRE</li></ol> | 262     | 22 AR309-4, AR242-3, AR217-3, AR252-5, AR170-2, AR265-2, AR365-2, AR 180-2, AR1171-2, AR282-2, AR3661, AR3151-1, AR1921-1, AR192-1, AR3082, AR277-2, AR106-1, AR3151-1, AR191-1, AR196-1, AR3081-1, AR186-1, AR291-1, AR3081-1, AR291-1, AR291-1, AR311-1, AR291-1, AR391-1, AR39 | 23 AR2353, AR275.3, AR221.3, AR282.2, AR201.2, AR291.2, AR180.2, AR286.2, AR173.2, AR178.2, AR225.2, |
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| HAIFLI8  HAJAN23  HAJAN23  HAJBR69  HAMFEI5                     | 640000     | 676933                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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|                                                                 | 01 111 411 | HAIFLIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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                                                                                                                                                                                   | HAJAN23 | HAJBR69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HAMFE15                                                                                              |

|    |         |         |     | AR175;1 L0748;10, L0754;9, L0731;9, L0766;8, L0439;7, L0803;6, H0624;5, L0739;5, S0356;4, H0486;4, H0090;4, H0789;4, L0438;4, L0749;4, L0736;4, L0777;4, L0599;4, S0360;3, H0013;3, S0003;3, L0394;3, L0794;3, L0704;4, L077;4, L0704;4, L077;4, L0704;4, L0704 |
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|    |         |         |     | L06893, L08093, L06653, H05393, L05623, S01142, S03582, S02782, H04412, H05862, H05332, H05812, H05822, H05332, H0592, L07702, L06622, L08642, L06662, L06622, H05422, H05422, H0592, H06702                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|    |         |         |     | 80330:2, L0747:2, L0750:2, L0755:2, L0758:2, L0589:2, L0592:2, L0581:2, L0593:2, S0276:2, S04242, H0170:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|    |         |         |     | H01711, S00401, S01161, H05801, H04581, H06381, H01921, S04181, S03541, S04101, H05801, S00461,<br>H03931, L07171, H04111, S60221, S02221, H05871, T01141, L00211, H03181, H04211, H00521, H05511,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | H0544:1, H0572:1, H0566:1, L0471:1, H0057:1, H0051:1, H0510:1, S6028:1, H0271:1, S0334:1, H0622:1, S0368:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | H0031:1, L0142:1, H0032:1, H0124:1, H0316:1, H0591:1, H0616:1, L0060:1, H0551:1, H0264:1, H0412:1, H0413:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | L0564:1, H0560:1, S0150:1, H0646:1, S0144:1, H0538:1, L058:1, L0538:1, L0743:1, L0771:1, L0521:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|    |         |         |     | LOGSO:1, LOSOS:1, LOGSS:1, LOGSS:1, LOGSS:1, HO144:1, SO3/4:1, HO691:1, HO520:1, HO689:1, HO658:1, HO658:1, HO672:1, SO163:1, HO630:1, HO638:1, HO638:1, HO638:1, HO638:1, HO638:1, HO638:1, HO648:1, HO6 |
|    |         |         |     | S0026.1, H0653.1, H0665.1, S0242.1, S0194.1, H0542.1, H0422.1 and H0422.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|    | HAMFE15 | 823350  | 263 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 14 | HAMGR28 | 892971  | 24  | AR271:8, AR184:7, AR060:7, AR240:6, AR089:6, AR219:5, AR104:5, AR183:5, AR225:5, AR275:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |         |         |     | AR266:5, AR316:5, AR274:5, AR192:4, AR053:4, AR267:4, AR096:4, AR247:4, AR277:4, AR309:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |         |         |     | AR312:4, AR283:4, AR248:4, AR253:4, AR186:4, AR182:4, AR185:4, AR238:4, AR299:4, AR310:3, AR289:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR285:3, AR313:3, AR213:3, AR218:3, AR291:3, AR241:3, AR039:3, AR251:3, AR286:3, AR033:3, AR2866:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |         |         |     | AR061:3, AR292:3, AR234:3, AR258:3, AR202:3, AR231:3, AR268:3, AR295:3, AR294:3, AR293:3, AR300:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR055:3, AR243:3, AR315:3, AR198:2, AR296:2, AR270:2, AR284:2, AR259:2, AR298:2, AR290:2, AR226:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR237:2, AR233:2, AR273:2, AR269:2, AR209:2, AR206:2, AR232:2, AR237:1, AR314:1, AR179:1, AR175:1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|    |         |         |     | L0666:11, H0046:9, H0556:5, L0809:5, L0747:4, L0770:3, L0769:3, L0783:3, H0520:3, L0439:3, L0731:3, H0664:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|    |         |         |     | S0045:2, H0123:2, H0424:2, L0637:2, L0775:2, S0328:2, S0146:2, L0777:2, L0601:2, H0542:2, L0411:1, H0265:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | H0740:1, H0294:1, H0583:1, H0650:1, H0662:1, S0420:1, S0444:1, H0637:1, H0735:1, S0476:1, S0278:1, H0370:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | H0586:1, H0587:1, H0497:1, H0486:1, H0013:1, H0069:1, H0575:1, H0533:1, H0581:1, H0251:1, H0150:1, T0010:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | H0083:1, H0239:1, H0594:1, H0288:1, H0290:1, H0604:1, H0553:1, H0040:1, H0087:1, H0494:1, H0560:1, L0065:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | 50438:1, 50440:1, H0641:1, H0633:1, H0646:1, L3815:1, S0422:1, S002:1, H0529:1, L0763:1, L0646:1, L0800:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|    |         |         |     | 10764:1, 10767:1, 10649:1, 10803:1, 10806:1, 10653:1, 10659:1, 10518:1, 10789:1, 10791:1, 80053:1, H0144:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | H0701:1, H0725:1, S0148:1, L0438:1, H0519:1, H0593:1, S0406:1, L0748:1, L0745:1, L0749:1, L0750:1, L0779:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    | HAMGR28 | 748223  | 264 | LOU 22.1, LOU 26.1, 500 21.1, 500 20.1, 500 400 1, and LOUOU.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| ž  | HAPRS03 | 557,959 | 35  | AR218-47 AR219-45 AR313-38 AR316-26 AR089-22 AR096-20 AR030-18 AR299-18 AR290-18 AR300-13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1  |         |         | ì   | AR104:13. AR240:11. AR055:11. AR277:10. AR060:8. AR283:8. S0422:15. L0766:8. H0014:6. L0005:5.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|    |         |         |     | 80360:5, L3827:5, H0657:4, L0789:4, H0413:3, L0646:3, L0805:3, L0655:3, L0777:3, L0591:3, S0242:3, H0543:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | L3643:2, S0442:2, S0376:2, L0770:2, L0764:2, L0649:2, L0650:2, L0775:2, L0659:2, L0783:2, L0663:2, L0665:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | L3822.2 H066c; L0751.2, L0747.2, L0758; 2, L056c; H0522.2, H0170:1, H056c; 1, S0420:1, S0354:1, H0637:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|    |         |         |     | S0045:1, H0/49:1, H0393:1, S0300:1, L0/17:1, L3816:1, H0346:1, H0042:1, H0375:1, H0004:1, H0318:1, H0052:1,<br>H0046:1 10157:1 H0017:1 H036:1 H036:1 H0644:1 H0180:1 H0068:1 H0038:1 T0067:1 H056:1:1 15475:1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| HBINSS8<br>HBINSS8<br>HBIFU48 |
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| M213-36, MROS-18, ARIGO-17, ARIGO-17, ARIGO-17, ARIGO-16, ARIGO-16, ARIGO-16, ARIGO-18, ARIGO-18 | MR2666, KR2453, AR1682, AR2462, AR2172, AR1772, AR2912, AR2642, AR2741, AR1651, AR2671,<br>AR3121, AR2161, AR3111, MR641, AR2611, AR1821, AR2991, AR2571, AR1661, AR2451, AR2991,<br>AR2981, AR2241, AR1751, L07663 and 101881. | RR2232, RR2712, KRP970, RR1991, RR1961, RR20611, RR20610, RR16110, RR26610, RR22910, AR21112, RR19911, RR19611, AR20611, AR20611, AR20611, AR20611, AR20611, AR20611, AR206110, | AR033-18, AR197-14, AR195-13, AR196-11, AR271-10, AR242-10, AR245-9, AR1659, AR201-9, AR207-9, AR1649, AR10482, AR1669, AR207-9, AR1649, AR1058, AR1786, AR1968, AR1988, AR2968, AR1988, AR298-1, AR1048, AR178, AR1989, AR298-1, AR2096, AR1989, AR298-1, AR298-1, AR299-6, AR1989, AR298-1, AR298-6, AR298 |
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| 33 | HCENK38 | 658737  | 43  | AR2215, AR222, AR242, AR232, AR802, AR802, AR229, AR212, AR2613, AR2612, AR262, |
| 4¢ | HCEWE20 | 543370  | 44  | MRZ538, ARBOSG, ARBOSG, ARBOSS, ARBOSS |
| 35 | HCFOM18 | 553582  | 45  | MRT194, ARBOSI, ARROSI, ARROSI, ARROSI, ARROSI, ARBOSI, ARROSIO, ARROSI, ARROSI, ARBOSI, ARROSI, ARBOSI, ARBOS |
| 36 | HCGMD59 | 636078  | 94  | AR2145, AR2154, AR2154, AR2154, AR2154, AR1223, AR1093, AR2073, AR2863, AR2863, AR1863, AR2863, AR2863 |

| WR2R25, ARMOS, ARBO94, ARMOSS, ARDGA, ARMOSA, ARMOSA, ARMOSA, ARMOSA, ARMOSA, ARMOSA, ARZASA, ARRASA, ARMOSA, |         |         | AR235:4, AR180:3, AR282:3, AR192:2, AR197:2, AR295:2, AR266:2, AR271:2, AR060:2, AR162:1, AR161:1, | AR163:1, AR170:1, AR089:1, AR169:1, AR257:1, AR216:1, AR217:1, AR168:1, AR277:1, AR225:1, AR311:1,<br>AR164:1, AR247:1, AR296:1, AR245:1 H0231:1 and S0216:1. | AR089:9, AR196:9, AR188:9, AR165:8, AR161:8, AR162:8, AR201:8, AR164:8, AR166:7, AR163:7, AR193:7, | AR1977, AR203:6, AR204:6, AR198:6, AR176:6, AR271:6, AR200:5, AR231:5, AR183:5, AR282:5, AR207:5, AR206:6, AD26:6, AD2 | AK182-4, AK190-4, AK255-4, AK237-4, AK287-4, AK181-4, AK256-4, AK261-4, AK299-4, AK257-4, AK195-4, | AR264:4, AR288:4, AR252:4, AR175:4, AR272:4, AR309:4, AR240:4, AR293:4, AR229:4, AR267:4, AR270:4, | AR179:3, AR290:3, AR316:3, AR286:3, AR061:3, AR275:3, AR234:3, AR217:3, AR178:3, AR172:3, AR177:3, | AR199:3, AR173:3, AR262:3, AR174:3, AR291:3, AR297:3, AR294:3, AR294:3, AR230:3, | AR2323, AR1853, AR2833, AR1893, AR2973, AR2953, AR23833, AR2683, AR1043, AR2262, AR1702, AR2133, AR2133, AR2803, AR2803, AR2703, AR2803, AR280 | AND 19.4 ANZZII.2 ANZWIJ, AND 21.4 ANZZII.2, ANZZII.4, A | DANESES, ANCESTE, ANC | H0156:1, H0046:1, H0622:1, L0483:1, H0674:1, S0440:1, L0372:1, L0364:1, L0805:1, L0663:1, S0374:1, S0434:1 and | L0599:1. |         | AR221:6, AR192:6, AR252:4, AR282:4, AR170:4, AR213:3, AR242:3, AR283:3, AR193:3, AR096:2, AR295:2, | AR309:2, AR243:2, AR274:2, AR313:2, AR181:2, AR164:2, AR223:2, AR226:2, AR201:2, AR272:2, AR166:2, | AR216:2, AR271:2, AR172:1, AR274:1, AR171:1, AR230:1, AR089:1, AR286:1, AR286:1, AR275:1, AR276:1, AR2 | AK228.1, AK238.1, AK165.1, AK311.1, AK162.1, AK180.1, AK205.1, AK168.1, AK288.1, AK2//.1 H0402.1, H0779.1 and L0747.1. | AR223-4, AR215-3, AR268-3, AR270-3, AR260-3, AR161-3, AR246-3, AR166-2, AR171-2, AR254-2, | ARZ1[12] ARZ132, ART   17.2] ARX0972, ARZ4212, ARZ4212, ARZ412, ARZ4222, ARZ6611, ARZ131, ART1911, ARX1911, ARX1911, ARX1911, ARX1021. A | ARCOLL, ARCOOL, 10789-4 10800-2 10759-2 10865-2 H0005-1 H0580-1 H0580-1 H0404-1 | H0559:1, H0486:1, H0031:1, H0674:1, H0135:1, H0100:1, L0800:1, L0794:1, L0804:1, L0805:1, L0515:1, L0783:1, | H06/2:1, L07/7:1, H0444:1 and H0352:1. | AR194:5, AR162:5, AR241:4, AR215:4, AR249:4, AR313:3, AR221:3, AR207:3, AR310:3, AR169:3, AR265:3, |
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| 37                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| 64 | HCWKC15 | 553621 | 53 | MR2293, AMB23, AKB282, ARB242, ARB242, ARB05, ARB205, ARB05, ARB05, ARB05, ARB233, AMB23, AKB23, AKB |
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| 4  | HCWUM50 | 639037 | 54 | MR1804, AR1654, AR1654, AR1665, AR3154, AR1623, AR1632, AR1632, AR3233, AR3092, AR3112, AR1952, AR2162, AR3752, AR652, AR9692, AR2562, AR2692, AR2692, AR3792, AR3791, |

| MRB1322, ARCHEGI, KAR (BGIS, KAR WOGE), KAR (BGIG, ARCHEGI, ARCHEG |         | MR29972, MR26423, AR25344, MR06573, MR06527, MR25323, MR05322, MR25225, MR26422, AR12134, MR26527, MR18426, MR26422, AR121341, MR26422, AR121341, MR26423, AR12141, AR16412, AR121413, AR16412, AR16412, AR164124, AR16414, AR164144, AR164144, AR164144, AR164144, AR164144, AR164144, AR164144444, AR1641444444, AR16414444444444444444444444444444444444 |         | AR03318, AR1041-14, AR253.11, AR1889, AR1868, AR2488, AR16646, AR2506, AR2235, AR1955, AR2895, AR28155, AR2155, AR2155, AR2816, AR2735, AR2816, AR28173, AR2814, AR2814, AR2814, AR2814, AR2813, AR2814, AR281 |
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|    |           |         |     | L0366:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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|    | HDPBI32   | 862851  | 279 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|    | HDPBI32   | 590733  | 280 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 48 | HDPCJ91   | 740748  | 28  | AR27486, AR216.79, AR214.77, AR205.65, AR225.63, AR245.61, AR24660, AR215.59, AR223.59, AR224.58, AR224.58, AR224.58, AR224.58, AR224.58, AR2175.3, AR2775.3, AR2175.3, AR2775.3, AR2175.3, AR275.54, AR2175.3, AR224.54, AR225.45, AR224.54, AR224.54 |
|    |           |         |     | AR165:40, AR271:40, AR221:37, AR096:37, AR254:37, AR164:37, AR166:36, AR247:36, AR309:36, AR299:35,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |           |         |     | AR163:35, AR210:33, AR161:32, AR162:32, AR253:32, AR236:30, AR311:30, AR316:29, AR173:29, AR199:28, AR060:38, AR160:39, AR100:37, AR10   |
|    |           |         |     | ARUNO 28, AR190:28, AR194:28, AR290:21, AR192:21, AR192:21, AR195:23, AR201:23, AR243:23, AR183:23, AR183: |
|    |           |         |     | AR219:22, AR291:22, AR240:22, AR267:22, AR288:20, AR290:20, AR295:20, AR300:20, AR180:20, AR193:19,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |           |         |     | AR277:19, AR178:19, AR177:19, AR268:19, AR296:19, AR266:18, AR269:18, AR266:18, AR264:18, AR297:18,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |           |         |     | AR293:17, AR242:17, AR191:17, AR261:17, AR262:17, AR231:17, AR255:16, AR203:16, AR237:16, AR200:16,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |           |         |     | AR181:16, AR176:15, AR289:15, AR182:15, AR104:15, AR270:15, AR232:14, AR230:14, AR285:13, AR287:13,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |           |         |     | AR033:13, AR257:13, AR239:13, AR28:13, AR061:13, AR207:12, AR234:12, AR260:12, AR065:12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|    |           |         |     | AR233:11, AR294:11, AR286:11, AR287:10, AR196:10, AR238:10, AR225::10, AR228:9 H0580:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|    |           |         |     | L0766;2, S01441, S0218;1, S0442;1, S0044;1, H033;1, H0013;1, S0474;1, H0581;1, S0388;1, S6028;1, H0266;1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| \$ | TIMBUL CO | 00000   | 5   | S01201; L0/91; L0/91; 10019; 10019; 10020; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 10070; 1 |
| 44 | HDPCL63   | 1019008 | 66  | AR28119, AR20213, AR40413, AR416114, AR416114, AR207113, AR206113, AR205113, AR2071, AR20712, AR20712, AR20712, AR20712, AR20712, AR20710, |
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|    |           |         |     | ARI 81.8 AR243.8 AR252.8 AR221.8 AR168.8 AR264.8 AR219.8 AR285.8 AR165.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|    |           |         |     | AR17657, AR1777, AR201.7, AR216.7, AR211.7, AR191.7, AR212.7, AR122.7, AR164.7, AR269.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|    |           |         |     | AR247:7, AR184:7, AR289:7, AR288:7, AR309:7, AR286:7, AR210:7, AR213:7, AR268:7, AR260:7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |           |         |     | AR287:7, AR189:7, AR292:7, AR053:7, AR266:7, AR104:6, AR173:6, AR204:6, AR297:6, AR283:6, AR272:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |           |         |     | AR290:6, AR236:6, AR182:6, AR312:6, AR308:6, AR180:6, AR096:6, AR277:6, AR188:6, AR293:6, AR186:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |           |         |     | AR299:6, AR190:5, AR052:5, AR300-5, AR199:5, AR199:5, AR291:5, AR089:5, AR249:5, AR291:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |           |         |     | AK294:3, AK248:3, AK214:3, AK316:3, AKU35:4, AK232:4, AK237:4, AK267:4, AK315:4, AK262:4, AK238:4,<br>  AR334:4 AR338:4 AR330:4 AR303:4 AR364:4 AR365:3 AR061:3 AR365:3 AR170:3 AR365:3 AR185:3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|    |           |         |     | AR256-3 AR277-3 AR260-3 AR270-3 AR278-3 AR278-3 AR278-3 AR278-2 AR278-3 AR278- |
|    |           |         |     | L0439:6, L0659:5, L0438:4, L0744:4, L0754:4, L0777:4, S0046:3, H0052:3, H0009:3, H0271:3, L0665:3, L0665:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |           |         |     | L0747:3, H0740:2, S0358:2, H0586:2, H0251:2, H0100:2, L3905:2, L0794:2, L0803:2, L0809:2, H0519:2, S0126:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |           |         |     | L0749:2, L0731:2, L0757:2, L0605:2, H0170:1, H0717:1, H0295:1, H0294:1, L0785:1, S0116:1, H0483:1, L3659:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |           |         |     | 80418:1, H0742:1, H0735:1, S0045:1, H0619:1, H0550:1, H0370:1, H0592:1, H0574:1, H0427:1, H0599:1, T0082:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |           |         |     | S0010-1, S0049-1, H0544-1, H0545-1, H0570-1, H0051-1, S0388-1, H0356-1, H0399-1, H026-1, H0622-1, L0194-1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|    |           |         |     | H01351, H04121, H06251, H00591, L03511, 100421, H05611, S02941, L06401, L47471, L55731, L55631,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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| HDPCIGS 897484 282 HDPCIGI 771583 61 HDPCIGI 771583 61 HDPHIS1 460679 62 HDPHIS1 879325 63 HDPMIS0 879325 63 HDPMIS0 695517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |    | HDPCL63 | 847045 | 281 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| HDPGT01 771583 61  HDPHIS1 460679 62  HDPM30 879325 63  HDPM30 603517 283  HDPM46 637386 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    | HDPCL63 | 897484 | 282 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| HDPM30 87932 63 HDPM30 603517 283 HDPM46 603517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 20 | HDPC025 | 460682 | 9   | AR060.2, AR055.2, AR282.2 H0521.2, H0445.2, H0394.1, H0747.1, H0581.1, L0761.1 and L0750.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| HDPIM30 879325 63 HDPIM30 63517 283 HDPIM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 51 | HDPGT01 | 771583 | 19  | AR268:5, AR244:4, AR282:3, AR251:3, AR242:3, AR241:3, AR052:3, AR184:2, AR271:2, AR310:2, AR176:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM50 879325 63 HDPIM50 603517 283 HDPIM50 603517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | AR194:2, AR039:2, AR309:2, AR283:1, AR178:1, AR289:1, AR217:1, AR257:1, AR277:1, AR170:1, AR284:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM51 460679 62<br>HDPIM50 879325 63<br>HDPIM50 603517 283<br>HDPIM56 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |    |         |        |     | AR221:1, AR226:1, AR265:1 H0521:3, S0278:2, S0222:2, H0284:2, H0265:1, H0728:1, S0007:1, H0208:1, H0586:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HDPIM30 879323 63 HDPIM30 693217 283 HDPIM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |         |        |     | H0497:1, H0642:1, H0581:1, H0052:1, H0572:1, H0024:1, H0292:1, H0428:1, H0628:1, H0135:1, H0163:1, H0433:1,<br> S0002:1, L2263:1, L0438:1, L3829:1, H0539:1, S0027:1, S0032:1, L0439:1, S0436:1, S0458:1 and H0352:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| HDPIM30 879325 63 HDPIM30 603517 283 HDPIM30 603517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 52 | HDPHI51 | 460679 | 62  | AR195:9, AR192:9, AR207:9, AR215:8, AR264:8, AR225:7, AR263:7, AR311:7, AR168:7, AR309:7, AR252:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPM30 603517 283<br>HDPM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |         |        |     | AR172:6, AR245:6, AR161:6, AR162:6, AR163:6, AR196:6, AR223:6, AR193:6, AR177:6, AR246:6, AR224:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 233<br>HDPIM30 663517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |         |        |     | AR197:5, AR308:5, AR272:5, AR214:5, AR275:5, AR222:5, AR253:5, AR176:5, AR261:5, AR295:5, AR291:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPM30 879325 63 HDPM30 603517 283 HDPM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |    |         |        |     | AR171:5, AR218:5, AR221:5, AR219:5, AR188:5, AR165:5, AR096:5, AR217:5, AR238:5, AR288:5, AR164:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 283<br>HDPIM30 663517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |         |        |     | AR175:5, AR166:5, AR089:5, AR271:5, AR060:4, AR240:4, AR183:4, AR201:4, AR257:4, AR169:4, AR312:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPM30 879325 63<br>HDPM30 603517 283<br>HDPM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |    |         |        |     | AR316:4, AR039:4, AR274:4, AR190:4, AR191:4, AR181:4, AR178:4, AR236:4, AR216:4, AR280:4, AR205:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 283<br>HDPIM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |         |        |     | AR210:4, AR270:4, AR170:4, AR277:4, AR243:4, AR235:4, AR212:4, AR104:4, AR199:4, AR189:4, AR242:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 283<br>HDPIM36 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |         |        |     | AR213:4, AR255:4, AR289:4, AR174:3, AR285:3, AR230:3, AR286:3, AR297:3, AR299:3, AR283:3, AR313:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 679325 63<br>HDPIM30 603517 283<br>HDPIM46 637386 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |         |        |     | AR204:3, AR287:3, AR173:3, AR247:3, AR229:3, AR269:3, AR296:3, AR182:3, AR293:3, AR266:3, AR258:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 283<br>HDPIM46 63517 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |         |        |     | AR198:3, AR237:3, AR262:3, AR033:3, AR239:3, AR185:3, AR231:3, AR203:3, AR200:3, AR179:3, AR211:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 283<br>HDPIM46 637386 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |         |        |     | AR227:3, AR268:3, AR267:3, AR294:3, AR290:3, AR234:3, AR232:3, AR226:3, AR300:2, AR280:2, AR282:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 879325 63<br>HDPIM30 603517 283<br>HDPIM46 675786 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |         |        |     | AR256:2, AR061:2, AR053:2, AR233:2, AR260:2, AR228:2, AR055:2 H0521:1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| HDPIM30 603517 283<br>HDPID46 637286 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 53 | HDPJM30 | 879325 | 63  | AR268:8, AR289:6, AR184:6, AR266:5, AR252:5, AR223:5, AR169:5, AR290:4, AR286:4, AR224:4, AR194:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPM30 603517 233<br>HDPM46 635786                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |    |         |        |     | AR257:4, AR214:4, AR310:4, AR270:4, AR165:4, AR294:3, AR291:3, AR222:3, AR183:3, AR235:3, AR215:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPM30 603:17 283<br>HDPM46 63:786 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |         |        |     | AR282:3, AR284:3, AR297:3, AR267:3, AR260:3, AR217:2, AR262:2, AR182:2, AR258:2, AR309:2, AR172:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPM30 603517 883 HDPM46 63786 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |    |         |        |     | AR288:2, AR298:2, AR225:2, AR269:2, AR296:2, AR176:2, AR248:2, AR166:2, AR216:2, AR250:2, AR292:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPM30 603:17 283<br>HDPM46 63:786 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |         |        |     | AR164:2, AR263:2, AR162:2, AR287:2, AR255:2, AR053:2, AR061:2, AR249:2, AR163:2, AR293:2, AR285:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 603517 283<br>HDPND46 637286 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | AR253:2, AR312:2, AR178:2, AR313:2, AR277:2, AR256:2, AR205:2, AR052:1, AR203:1, AR238:1, AR274:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 603517 283<br>HDPND46 637586 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | ARI71:1, AR295:1, AR247:1, AR247:1, AR206:1, ARI81:1, AR221:1, AR226:1, AR230:1, AR179:1, AR283:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 603517 283<br>HDPND46 637586 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | AR232:1, AR200:1, AR239:1, AR186:1, AR237:1, AR195:1, AR228:1, AR240:1, AR233:1, AR245:1, AR246:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HDPIM30 603517 283<br>HDPND46 637586 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | AR199:1, AR173:1, AR243:1, AR243:1, AR177:1 L0800:4, H0617:3, H0521:3, L0070:3, L0742:3, L0770:2, L0771:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HDPIM30 603517 283<br>HDPND46 637586 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | 1.0742. 106892. 1074.12. 1043.22. 10445.2. 104242.1 10637.1, 10370.1 10320.1 10022.1, 10194.1, 10455.1, 10455.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| HDPJM30 603517 283<br>HDPND46 637586 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |         |        |     | S0422:1, L0761:1, L0764:1, L0806:1, L0659:1, L5622:1, L0789:1, L0790:1, L0792:1, H0672:1, S0152:1, S0454:1 and<br>S0436:1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| HDPND46 637586 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |    | HDPJM30 | 603517 | 283 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AR264-5 AR165-5 AR161-5 AR217-5 A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 54 | HDPND46 | 985/59 | 64  | AR252:7, AR170:6, AR223:6, AR207:6, AR311:6, AR165:6, AR263:5, AR162:5, AR163:5, AR164:5, AR214:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Parameter (Caracacacacacacacacacacacacacacacacacaca                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |    |         |        |     | AR264:5, AR195:5, AR161:5, AR212:5, AR308:5, AR225:4, AR166:4, AR242:4, AR250:4, AR053:4, AR217:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|    |         |         |     | AR2244, AR1934, AR1693, AR2723, AR2163, AR2363, AR3123, AR6893, AR2823, AR3993,<br>AR1723, AR1973, AR2653, AR1803, AR3133, AR2613, AR2113, AR1683, AR2053, AR2773, AR2413,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|    |         |         |     | AR2973, AR2743, AR2133, AR1993, AR1813, AR1963, AR2013, AR2452, AR2953, AR1982, AR2752,<br>AR2882, AR1742, AR2472, AR2062, AR2152, AR1762, AR2712, AR1752, AR1713, AR1782, AR2462,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR188:2, AR300:2, AR200:2, AR203:2, AR033:2, AR096:2, AR104:2, AR310:2, AR296:2, AR060:2, AR257:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR295.2, AR286.2, AR189.2, AR287.2, AR204.2, AR191.2, AR262.2, AR270.2, AR183.2, AR273.2, AR239.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AK210'2, AK209'2, AK240'2, AK19'22, AK28'2, AK216'2, AK185'2, AK2112, AK118'3, AK244'2, AK19'22, AK218'2, AK18'3'2, AK2112'3, AK18'3'2, AK218'3'2, AK218'3'2, AK218'3'3, AK218'3'3, AK218'3'3, AK218'3'3, AK218'3'3, AK218'3'3, AK218'3'3'3'3'3'3'3'3'3'3'3'3'3'3'3'3'3'3'3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | AR255:1, AR265:2, AR256:2, AR266:2, AR190:2, AR193:1, AR295:1, AR17:1, AR265:1, AR39:1, AR266:1, AR255:1, AR266:1, AR266 |
|    |         |         |     | AR182:1, AR227:1 H0522:2 and L0055:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 55 | HDPOJ08 | 731863  | 99  | AR250:19, AR254:19, AR269:19, AR268:16, AR248:16, AR290:15, AR249:13, AR270:12, AR253:12, AR183:10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |         |         |     | AR267:10, AR180:10, AR161:9, AR162:9, AR165:9, AR164:9, AR163:9, AR181:8, AR166:8, AR173:8, AR174:8,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|    |         |         |     | AR184:7, AR235:7, AR252:7, AR229:7, AR272:7, AR176:7, AR177:6, AR178:6, AR265:6, AR239:6, AR182:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR175:6, AR096:6, AR281:5, AR189:5, AR287:5, AR190:5, AR261:5, AR263:5, AR179:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|    |         |         |     | AR228:5, AR286:4, AR234:4, AR257:4, AR193:4, AR238:4, AR285:4, AR289:4, AR289:4, AR885:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |         |         |     | AR311:4, AR286:4, AR286:4, AR282:4, AR282:4, AR240:4, AR232:4, AR201:4, AR261:4, AR262:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |         |         |     | AK089:4, AR210:4, AR212:4, AR295:4, AR247:4, AR297:4, AR275:4, AR262:4, AR295:4, AR195:4, AR188:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR231:4, AR197:4, AR309:4, AR196:4, AR284:4, AR191:4, AR299:4, AR313:3, AR255:3, AR199:3, AR200:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR293:3, AR300:3, AR316:3, AR296:3, AR246:3, AR203:3, AR243:3, AR294:3, AR214:3, AR274:3, AR104:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR060:3, AR219:3, AR298:3, AR033:3, AR227:3, AR053:3, AR221:2, AR271:2, AR312:2, AR218:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|    |         |         |     | AR061:2, AR259:2, AR224:2, AR217:2, AR277:2, AR225:2, AR258:2, AR215:2, AR039:2, AR168:2, AR266:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR211:2, AR055:2, AR222:2, AR205:2, AR216:2, AR202:1, AR213:1, AR260:1, AR256:1, AR314:1 S0474:29,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | L0766:11, H0521:10, L0803:7, L0748:6, L0717:5, L0759:5, S0003:4, L3832:4, H0663:3, H0156:3, L0598:3, L0770:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|    |         |         |     | L0771:3, L0804:3, L2439:3, H0522:3, L0731:3, S0436:3, H0486:2, S0426:2, L0805:2, L0659:2, L2260:2, S0126:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | S0406:2, L0749:2, L0755:2, L0757:2, L0758:2, L0590:2, S0026:2, H0716:1, H0341:1, S0212:1, L0481:1, S0444:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | S0360:1, L3649:1, H0637:1, H0580:1, H0734:1, H0749:1, L3092:1, H0619:1, L3388:1, H0586:1, H0574:1, H0427:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | 1,0021:1, H0575:1, H0318:1, H0545:1, H0024:1, H0373:1, H0071:1, H0179:1, S0214:1, H0428:1, H0674:1, H0591:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|    |         |         |     | H0616:1, H0488:1, H0494:1, S0438:1, S0440:1, H0647:1, S0142:1, UNKWN:1, L0369:1, L0763:1, L0769:1, L0646:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | L0648:1, L0662:1, L0650:1, L0775:1, L0653:1, L0776:1, L0656:1, L0782:1, L0809:1, L0519:1, S0052:1, L2637:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | H0144:1, L3823:1, H0520:1, H0547:1, H0660:1, S0380:1, L0742:1, L0439:1, L0750:1, L0777:1, S0031:1, H0445:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|    |         |         |     | S0434:1, H0665:1, H0667:1, S0194:1, S0276:1 and S0458:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 99 | HDPPN86 | 1037893 | 99  | /AR212:4, AR235:3, AR266:2, AR221:2, AR207:2, AR205:2, AR216:2, AR168:2, AR282:2, AR257:2, AR181:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    |         |         |     | AR311:1, AR271:1, AR161:1, AR264:1, AR165:1, AR172:1, AR295:1, AR164:1, AR162:1, AR176:1, AR163:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|    |         |         |     | AR171:1, AR285:1, AR289:1, AR277:1, AR238:1, AR089:1, AR234:1, AR211:1 H0542:4, S0418:3, H0543:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|    |         |         |     | S0038:2, H0341:1, L0018:1, H0069:1, H0090:1, H0056:1, H0494:1, H0522:1 and H0423:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|    | HDPPN86 | 895711  | 284 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 22 | HDPSB18 | 1043263 | 29  | AR197-9, AR060:8, AR253:8, AR161:8, AR162:8, AR163:8, AR165:8, AR164:7, AR089:7, AR166:7, AR204:7, AR197-9, AR197-6, AR1 |
|    |         |         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| ARB252, ARB92, ARB92, ARB92, ARB52, ARB52, ARB52, ARB62, ARB62, ARB82, ARB152, ARB52, ARB92, |         | AR2D231, ARBORS A, ARVELS A, (RROPE), ARBORS A, RAD2S32, ARBORS A, RRUPS A, |         | MITTING ARTHERIS ARTHERIS ARTISTS ARTESTS ARTESTS ARTHERS ARTHERIS |
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                                              | HDPSP01 | HDPSP54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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|    |         |        |    | KROB93, ARSES, ARWBS, ARE752, ARRODS, ARROS, ARROS, ARGROS, ARROS, ARZOS, ARZOS, ARZOS, ARZOS, ARZOS, ARGOS, ARGOS, ARZOS, ARZOS, ARZOS, ARGOS, ARGOS |
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| 62 | HDPUW68 | 812737 | 72 | MARCES 15, ARRIST 4, ARCITST, MARCH 11, ARCISSA, KARIPO9, ARCISSA, RABIGSA, ARCSTS, ARCHES, ARCSTS, ARCHES, AR |
| 63 | HDPWU34 | 630354 | 73 | KARCHIS, ARBORI, ARBORI, ARBHISH RAGESTI, ARCHISTILL ARCESTILL ARCHIST, ARC |

|    |                 |         |     | S0260:1 and S0436:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|    | HDPWU34         | 701979  | 292 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 64 | HDPXY01         | 879048  | 47  | MRDDR, ALGES, MUZES, AULES, ARIGHA, ARIGHA, ST.S., ARIGEA, S.R. ARIGEA, S.R. RISSA, ARIGEA, ARIGEA, MRDDR, ARIGEA, ARI |
|    | HDPXY01         | 904768  | 293 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|    | HDPXY01         | 895716  | 294 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|    | HDPXY01         | 895715  | 295 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 99 | HDTBV77 HDTBQ23 | 1306984 | 75  | AR1837, AR1845, AR2094, AR2074, AR2074, AR1824, AR2144, AR1724, AR2234, AR2633, AR2733, AR2734, AR2643, AR2734, AR2643, AR2734, AR2643, AR2734, AR2643, AR2743, AR274, AR2743, |

| RAZD64, ARD973, AR1924, RAZD34, ARZD94, ARZD94, ARZD94, ARZD94, ARZD94, ARZD64, ARZD614, ARZD97, ARZD923, ARZD53, ARZD53, ARZD614, ARZD95, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD94, ARZD62, ARZD93, ARZD93, ARZD94, ARZD62, ARZD92, ARZD93, ARZD94, ARZD62, ARZD92, ARZD93, ARZD94, ARZD62, ARZD92, ARZD93, ARZD94, ARZD62, ARZD92, ARZD92, ARZD92, ARZD92, ARZD94, ARZD62, ARZD92, ARZD92, ARZD92, ARZD92, ARZD92, ARZD92, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD93, ARZD94, ARZD92, ARZ |         |         | MR22915, AR2215, AR22172, AR22911, AR22211, AR2223, AR2194, AR2155, AR2155, AR2155, AR2155, AR2155, AR2152, AR2171, AR2294, AR2166, AR2166, AR2166, AR2166, AR2166, AR2166, AR2166, AR2166, AR2164, AR |         | AR2356, AR2024, AR3094, AR1714, AR2704, AR1783, AR2723, AR2453, AR2603, AR2913, AR1693, AR2863, AR28133, AR2133, AR2243, AR2673, AR2863, AR2874, AR267, AR1773, AR2633, AR283, AR2863, AR2813, AR2920, AR1612, AR1812, AR3082, AR3002, AR2572, AR2822, AR1612, AR1812, AR2062, |
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                                               | 596     | 297     | 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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| 69 | не2Рн36 | 570903 | 79 | AR2144, ARB514, AR17234, AR12154, AR12248, AR12857, AR2135, AR1214, AR6194, AR21723, AR2144, AR6194, AR172534, AR127234, AR21944, AR61944, AR6194, AR172534, AR21723, AR21944, AR8194, AR21943, AR2194, AR2194 |
| 70 | HEBDS15 | 847060 | 08 | ARRWOTT, ARRIET, ARRIVAT, NROWER, 4 RATELLE, JARTINE, ARKIVETIA, RATELL, ARRISTLA, RARRY ARRY OLD ARRY |
| 71 | HE9C069 | 596829 | 8  | AR275:30, AR205:25, AR039:23, AR207:23, AR309:18, AR162:16, AR161:16, AR163:16, AR264:15, AR197:15, AR089:14, AR165:14, AR198:14, AR166:13, AR166:13, AR166:13, AR166:13, AR166:13, AR166:13, AR166:13, AR166:13, AR166:14, AR166: |

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|    |         |         |     | MRZPS2, AR033-2, AR299-2, AR299-2, AR2712, AR397-2, AR275-2, AR274-2, AR231-2, AR299-2, AR231-2, AR274-2, AR6062, AR6962-2, AR6062, AR6962-3, AR69 |
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|    | HE90W20 | 838598  | 599 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|    | HE9OW20 | 834400  | 300 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 74 | HEEAG23 | 684254  | 84  | AR313.22, AR099.19, AR299-16, AR089-15, AR277.14, AR300-11, AR104-11, AR060-11, AR185-11, AR096.11, AR316-01, AR085.9, AR318-01, ARAS19, AR295-16, AR296, AR316-01, AR318-01, AR |
|    |         |         |     | 80420.1, 80404.1, 107947.1, 107951.1, 23111.3, 80400.1, 80278.1, 10849.1, 10054.1, 10054.1, 10794.1, 10796.1, 10704.1, 10794.1, 10794.1, 10796.1, 10774.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 10787.1, 1 |
| 75 | неом063 | 603533  | 82  | WR0997, AR221-4, AR271-4, AR809-3, AR803-3, AR81-3, AR |
| 76 | HEPAB80 | 1307790 | 98  | ARI 1911, 7-184099, ARD-84579, ARITO-6, ARIC 645, ARIS 1966, ARIS 1966, ARIS 1966, ARIS 1866, ARIS 1865, ARIS 1865, ARIS 1865, ARIS 1875, ARIS  |
|    | HEPAB80 | 570048  | 301 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 11 | HFABG18 | 847073  | 87  | AR292:14, AR186:12, AR241:10, AR194:9, AR273:9, AR052:8, AR202:8, AR061:8, AR282:7, AR291:7, AR206:7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| MRT03   MRT0 |
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|    |                  |        |     | [10373:1, S0021:1, S6028:1, H0615:1, L0794:1, L0804:1, S0126:1, H0436:1, S0028:1, L0756:1, L0777:1, L0731:1 and S0242:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| 88 | HFXBL33          | 778070 | 86  | ARI (1623, ARICE)4, ARI (1624, ARISE)32, ARI (1517, ARICE)7, ARI (1614, ARI)51, ARI (1614, ARIZO)14, ARIZO)14, ARIZO)14, ARIZO)14, ARIZO)14, ARIZO)14, ARIZO)16, ARIZO)19, ARIZO 16, ARIZO)10, ARIZO 16, ARIZO 17, ARIZO 18, A |
| 68 | нғхнк <i>т</i> з | 609826 | 66  | ARRIGE, SARIGES, KRIGES, KRIGES, ARROPA, ARROSA, ARROSA, ARROGA, ARRIGES, ARRIGES, ARRIGES, ARROSA, AR |
| 06 | HFXJX44          | 701988 | 001 | MRB1313, MRGE11, MRIGE11, MRIB191, MRIGE10, MRIPG10, MRB310, MRIGE3, MRR93, ARRIE39, MRR193, MRR193, MRR193, MRR194, MR293, MRR194, MR293, MRR194, MR293, MRR194, MR293, MRR194, MR293,  |
| 16 | HFXKY27          | 634161 | 101 | AR2823, AR2253, AR1763, AR2303, AR2703, AR1733, AR1643, AR1653, AR1723, AR1663, AR2573, AR1613, AR1752, AR1782, AR1622, AR1632, AR3692, AR2692, AR2692 |

|    |         |        |     | ARBIB-2, ARZB-2, ARZB-2, ARZB-2, AR47-2, ARB9-2, ARZB-2, ARBID-2, ARZB-2, ARZB-3, ARZB-2, ARZB-3, ARZB-2, ARZB-3, ARZB-2, ARZB |
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| 92 | новизз  | 570262 | 102 | WAGE-1, ARGEST, ARGEST, RASSET, HELEZYS WILLEZYS BINDS, ARGEST, ARGEST |
| 6  | HGLAF75 | 566838 | 103 | ARTIORS, ARAGES, ARRISES, ARRI |

| AR2166, AR2294, AR2991, AR9096, AR2246, AR2176, AR9276, AR3216, AR2246, AR2246, AR236, AR364, AR236, AR364, AR236, AR364, AR236, AR364, AR236, AR364, AR236, AR3676, AR36776, AR3676, AR36776, AR3676, AR3676, AR3676, AR36776, AR3676, AR36776, AR3676, AR36776, AR3676, AR36776, AR367776, AR36776, AR36776, AR36776, AR36776, AR36776, AR36776, AR367776, AR36776, AR36776, AR367776, AR36776, AR36776, AR36776, AR36776, AR36776, AR36776, AR36776, AR367776, AR36776, AR367776, AR36776, AR36776, AR367776, AR36776, AR36776, AR36776, AR367776, AR |         |         | AR1992, AR1994, AR1717, AR2734, AR1917, AR1917, AR2794, AR2805, AR1956, AR1966, AR1966, AR1966, AR1969, AR1969, AR1916, AR1916 |         | AR2423, AR2353, AR1833, AR3093, AR2823, AR2432, AR1712, AR2831, AR0551, AR2571, AR1681,<br>AR2131, AR1641, AR2301, AR2641, AR2871, H05432, H04971 and H06251. | AR2214, AR2355, AR1803, AR1923, AR2773, AR2523, AR2452, AR2152, AR1852, AR3082, AR2162, AR2162 | NR241-5, AR249-5, AR310-5, AR186-4, AR251-4, AR052-4, AR282-3, AR171-3, AR055-3, AR309-3, AR224-3, AR171-5, AR037-3, AR348-2, AR348-2, AR357-2, AR188-2, AR857-2, AR189-2, AR189-2, AR189-2, AR189-2, AR189-2, AR28-2, AR26-2, AR206-2, AR206-2, AR207-2, AR199-2, AR28-2, AR29-2, AR2 |
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| 1003028                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 883427  | 847543  | 638231                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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                                               | HHBCS39 | HHBCS39 | HHEAA08                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HHEAA08 | HHENV10                                                                                                                                                       | HHFFJ48                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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| 46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| MR2951, MR2661, MR1661, MR2961, MR2913, MR2913, MR2981, MR691, MR2914, | MRT734, AUST313, ARIGHT, ARICS12, MRG612, ARICS12, ARIGG14, MRT511, ARIGG11, ARICG11, ARICG11, ARICG14, ARICG16, ARICG16 | D. MRI923, ARRIG-3, ARRIG-3, ARRIG-3, ARBOS, ARD45, ARRIG-3, ARRIG | NR2954, NR 1975, AR 1895, GAR 1976, AR 1966, AR 1916, AR 181746, AR 1906, AR 1824, AR 1825, AR 1935, AR 1975, A |
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|     |         |        |     | AR22551, AR241, AR2581, AR2281, AR2291, AR2710, AR2101, LOURSE, GROSZ+1 GROSZ-1, GROSS-3, H05742, H0592, L07622, L08092, L07622, L08092, L07622, L08092, L07622, L08092, L07622, L08092, L07622, L0762 |
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|     | HHGCM76 | 383547 | 307 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 102 | HHGCQ54 | 544615 | 112 | MRD154, ARBA, ARBA, ARBOS, ARB |
| 103 | ППРЕМ62 | 695134 | 113 | MARIO 6529, ARD 65212, ARD 652115, ARD 19715, ARD 19727, ARD 1973, ARD 65223, ARD 65224, ARD 652216, ARD 65224, ARD 65224 |
| 104 | HJABB94 | 456466 | 114 | AR176:9, AR225:9, AR221:8, AR295:8, AR170:8, AR264:8, AR178:8, AR288:7, AR291:7, AR180:7, AR215:7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| MR175; AR275; AR977; AR274; AR274; AR275; AR295; AR296; AR306; AR270; AR205; AR295; AR295; AR295; AR1025; AR295; AR1025; AR1025; AR295; AR1025; AR1025; AR295; AR1025; AR295; AR1025; AR295; AR1025; AR295; A | AR209-73. AR203-3. AR203-2. ARC653_2. ARC6429. AR229-34. AR210-24. AR609-28. AR207-77. AR222-27. AR209-73. AR210-74. AR210-74. AR210-74. AR210-74. AR210-74. AR210-75. AR210-75. AR210-75. AR210-75. AR200-74. AR200-74. AR210-75. AR210-75. AR200-74. AR200-74. AR210-75. AR200-74. |         | ARDES, AR HIGES, AREN HIGE, AR HIGE, AR WILDER, ARRIES, ARRIEG, ARZIES, ARRIES, ARZIES, ARZIES |
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                                                                                              | HJACG02 | HJACG30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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|     |         |        |      | [H0318:1, L4747:1, L0646:1, L0766:1 and L0803:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|     | HJACG30 | 821341 | 309  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     | HJACG30 | 774300 | 310  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 107 | HIBCY35 | 719729 | 1117 | MRZD511, MRZD510, MRZD50, MRZD9, MRZD66, MRD504, MRZD78, MRZD67, MRZD7, MRZD7, MRZD7, MRZD7, MRZD7, MRZD96, MRZD6, MRZD66, MRZD56, MRZD66, MRZD56, MRZD66, MRZD56, MRZD64, MRZD56, MRZD64, MRZ |
| 108 | HIPAD75 | 651337 | 118  | WR2777, AR2612, AR262, AR262, AR2622, AR2622, AR172, AR172, AR1661, AR1621, AR1671, AR1661, AR2611, AR |
| 109 | HKABZ65 | 862030 | 119  | WRB1941, ARB292, KUR992, KR MISSTS ARRIESZA, KR MEIG-24, KR MISC-24, KR MISS-24, KR WRS-24, KR WR                                                                                                                                                          |

| HKACDS8 1852202 120 HKACDS8 1852202 120 HKACDS8 552465 312 HKACDS8 157263 121 | AR311.7, AR167, AR2677, AR1727, AR2867, AR2337, AR2057, AR1716, AR2276, AR1686, AR2146, AR2016, AR2016, AR2016, AR2016, AR2016, AR2016, AR2016, AR2016, AR2016, AR20165, AR201 |        | AR28712, AR2529, AR2929, AR2927, AR8917, AR28816, AR28618, AR28618, AR28618, AR28618, AR28712, AR2811, AR28611, |        | MRZDSZA, KNIESSI, AKUSJA, AKUSJA, RIGISZA, KNIESZA, KNIESZA, ZAKUSZA, ZAKUSZA, KARZDSZA, KNIESZA, KNIE |
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| HKAEDS8 HKAEDS8 HKAEV06                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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|     |         |         |     | S0440:1, L3815:1, L0800:1, L0662:1, L5574:1, L0803:1, L0776:1, L0659:1, L2655:1, L2653:1, S0374:1, H0547:1, H0647:1, S0330:1, H0521:1, H0696:1, L0439:1, L0752:1, L0594:1 and H0543:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|     | HKAEV06 | 638238  | 313 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 112 | HKAFT66 | 946512  | 122 | MRR14-23, MRR19-28, MRR21-24, MRR21-25, MRR24-25, ARR85-23, MRR21-21, MRR21-23, MRR21-21, MRR21- |
|     | HKAFT66 | 889258  | 314 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     | HKAFT66 | 904190  | 315 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 113 | HKB1E57 | 876571  | 123 | MR254, AR223, AR1713, MR2053, AR1923, AR1643, AR2542, AR2672, AR271, AR1714, AR193, AR2712, AR1632, AR1672, AR1612, AR1632, AR1612, AR1632, AR1612, AR1614, AR2711, AR |
|     | HKB1E57 | 654871  | 316 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 114 | HKFBCS3 | 1352286 | 124 | MR299455. ACRASH 511, MR251-III ARASS54, AR2534, AR2632, AR264-II 8, AR29015, AR28851, AR264-II 8, AR27011, AR28851, AR264-II 8, AR27011, AR28851, AR264-II 8, AR27011, AR2895, AR27011, AR2901, AR2895, AR27011, AR2901, AR29 |

|     |                 |                            |                   | jinoon, jinazya, jinaya; jinooya; 80142;, 8042s, jinokab; Liofks; Lioffo; Lioffo; Liogos; Liokob; Liogos; Liog |
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|     | HKFBC53         | 701893                     | 317               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     | HKFBC53         | 513190                     | 318               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     | HKFBC53         | 383426                     | 319               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 115 | HKGDL36 HKGDL36 | 877489<br>704088<br>625956 | 125<br>320<br>126 | WR22493, ARIBGAZJ, ARIBGAZJ, ARUGUGZ, ARDAG, ARAZLAGO, ARZLAGO, ARZLZIG, RARZZIG, ARUGUGZ, ARRIPGIS, ARZLAG, |
| 0   | HKINBS          | 056570                     | 871               | MR 101-1, ARROYL, ARROYL, ARROYL, ARRIVAN, ARRONA, ARROYA, ARR |
| 117 | HKMMW74 581399  | 581399                     | 127               | AR229:11, AR313:11, AR163:10, AR162:10, AR161:10, AR242:9, AR176:9, AR039:9, AR204:9, AR197:8, AR309:8,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|             |         |     | AR192:8, AR180:8, AR264:8, AR181:8, AR178:8, AR089:8, AR177:8, AR164:8, AR247:7, AR268:7, AR196:7, AR239:7, AR239:7, AR239:7, AR231:7, AR246:7, AR23:7, AR30:7, AR269:7, AR233:7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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|             |         |     | AR173:7, AR174:7, AR179:7, AR267:6, AR236:6, AR238:6, AR175:6, AR179:6, AR096:6, AR096:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|             |         |     | AR299:6, AR235:6, AR257:6, AR240:6, AR261:6, AR055:6, AR293:6, AR275:6, AR226:5, AR237:5, AR185:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | /ARI83:5, AR243:5, AR201:5, AR234:5, AR195:5, AR250:5, AR207:5, AR291:5, AR245:5, AR316:5, AR266:5,<br>AR101:5, AR317:5, AR053:5, AR277:5, AR231:5, AR254:5, AR230:5, AR2567:5, AR270:5, AR204:4, AR224:5, AR204:4, AR204:5, A |
|             |         |     | AR289:4, AR263:4, AR285:4, AR212:4, AR193:4, AR199:4, AR288:4, AR216:4, AR218:4, AR213:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|             |         |     | AR255:4, AR217:4, AR297:4, AR277:4, AR200:4, AR104:4, AR272:4, AR232:4, AR205:4, AR274:4, AR296:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | AR295:3, AR286:3, AR033:3, AR189:3, AR287:3, AR290:3, AR256:3, AR190:3, AR311:3, AR283:3, AR169:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | AR168.3, AR170.3, AR215.3, AR253.3, AR308.3, AR388.3, AR188.3, AR171.3, AR214.3, AR223.3, AR219.2, AR204.7, AR204.7, AR201.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 118 HLDNA86 | 1352197 | 128 | AR314;215, AR280;182, AR186;162, AR298;160, AR315;158, AR241;158, AR259;155, AR227;154, AR055;144,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | AR233:143, AR281:140, AR275:136, AR232:134, AR192:131, AR061:131, AR175:130, AR284:127, AR194:125,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | AR204:120, AR295:120, AR237:117, AR285:116, AR033:112, AR286:111, AR184:108, AR185:107, AR226:107,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | AR238:107, AR293:105, AR177:100, AR198:100, AR231:100, AR299:100, AR300:99, AR206:99, AR202:97,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|             |         |     | AR271:95, AR052:94, AR273:91, AR104:84, AR243:84, AR179:83, AR292:80, AR294:77, AR283:71, AR291:71,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR229:68, AR244:67, AR282:66, AR267:63, AR234:63, AR053:61, AR182:60, AR039:59, AR310:57, AR205:57,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR183:56, AR274:56, AR060:51, AR089:49, AR247:49, AR296:48, AR251:46, AR240:46, AR269:46, AR309:45,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR316:45, AR213:43, AR258:42, AR096:40, AR246:39, AR289:38, AR265:38, AR290:37, AR268:36, AR270:36,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR211:35, AR256:34, AR312:33, AR277:32, AR161:32, AR162:32, AR218:32, AR228:31, AR163:29, AR239:29,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR266:29, AR248:28, AR262:27, AR203:27, AR174:27, AR219:26, AR199:26, AR249:25, AR230:25, AR287:23,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR195:23, AR311:22, AR191:22, AR190:22, AR263:21, AR236:21, AR313:21, AR288:21, AR181:20, AR253:20,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR257:20, AR196:19, AR193:19, AR188:19, AR201:19, AR210:19, AR255:17, AR176:17, AR200:17, AR189:17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR264:17, AR178:17, AR272:16, AR260:15, AR261:14, AR173:14, AR297:14, AR197:14, AR212:12, AR180:12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|             |         |     | AR165:11, AR164:11, AR235:11, AR166:10, AR207:10, AR254:9, AR250:9, AR221:7, AR245:7, AR216:7, AR308:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|             |         |     | AR242:6, AR169:6, AR215:6, AR217:5, AR252:5, AR172:4, AR225:4, AR224:4, AR223:3, AR222:3, AR214:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|             |         |     | AR168:2, AR171:2, AR170:1 L0758:10, L0731:8, L0747:7, H0545:6, L0769:6, L0809:6, L0740:6, L0803:5, L0775:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | L0748:5, L0755:5, S0360:4, L0749:4, L0757:4, S0358:3, H0722:3, L0771:3, L0774:3, L0657:3, L0782:3, L0788:3, L078:3, L0    |
|             |         |     | 10049'2, H0538'2, S02/8'2, H0509'2, H0266'2, S0438'2, H052'2, L07/8'2, L07/8'2, L07/9'2, L0518'2, L0666'2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|             |         |     | S012622, S0027:2, L0743:2, L0751:2, L0756:2, L0753:2, L07593:2, L0593:2, S0192:2, H0624:1, H0171:1, H0556:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|             |         |     | L3644:1, S0040:1, H0717:1, H0295:1, H0484:1, H0661:1, H0305:1, S0418:1, S0442:1, S0408:1, H0730:1, H0747:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | H0393:1, H0441:1, H0333:1, H0574:1, H0486:1, T0040:1, L3657:1, S0280:1, H0746:1, L0738:1, H0530:1, H0544:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | H0046:1, H0041:1, H0571:1, H0123:1, H0024:1, H0510:1, S0314:1, S0003:1, H0622:1, T0006:1, H0644:1, H0617:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | H0673:1, H0135:1, H0163:1, H0634:1, H0616:1, H0551:1, S0144:1, S0142:1, S0422:1, L0520:1, L0763:1, L0638:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | L5565:1, L3905:1, L0373:1, L0644:1, L0648:1, L0766:1, L0804:1, L0375:1, L0805:1, L0653:1, L0776:1, L0659:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | L5622:1, L0663:1, L0665:1, H0651:1, S0044:1, H0555:1, S3012:1, S0390:1, S3014:1, L0750:1, S0026:1, H0653:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|             |         |     | S0194:1, H0543:1, H0423:1, S0462:1 and H0721:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HLDNA86     | 535730  | 321 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|         | ARRIEGA ARRICAS, ARRICAS, ARRIGES, RARIGAS, ARRIGAS, ARRISTA, ARRIOTA, ARRI | MR3538, ARTITJ, AR2456, AR245, AR1855, AR2655, AR2644, AR2694, AR2694, AR0694, AR18694, AR18634, AR1624, AR2684, AR1614, AR1614, AR16194, AR27194, AR16195, AR27194, AR16194, AR27194, AR16194, AR27194, AR16194, AR18194, AR18194, AR18194, AR18194, AR2719, AR2723, AR2723, AR2724, AR18194, AR18194, AR18194, AR18194, AR28194, AR29194, AR18194, AR18194, AR18194, AR18194, AR28194, AR29194, AR18194, AR18194, AR18194, AR18194, AR28194, AR29194, AR18194, AR18 |
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|         | 753742                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 740755                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| HLDON23 | HLDQR62                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HLDQU79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 611     | 120                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 121                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| 123 122 | HLHAL68 HLIBD68 | 684216<br>778073 | 132 | MRITTO, MR WER, ARROIT, ARRIPAT, ARRIPAT, ARRIPAT, ARRIPAT, ARRIPAT, ARROIT, ARRIPAT, ARROIT,  |
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| 124     | HLICQ90         | 791828           | 134 | MRD2639, MRD2546, MRD2546, ARZH666, ARZH646, ARZH164, ARD8484, ARD8552, ARZH636, ARZH246, ARZH246, ARZH246, ARZH246, ARZH246, ARZH246, ARZH246, ARZH246, ARZH247, ARZH246, ARZH246, ARZH247, ARZH246, ARZH246, ARZH247, ARZ |

| ARIDELI, AREDGIT, AREDGIT, ARIDGIT, ARIDGIT, ARIDGIT, ARIDGIT, ARIBGIT, ARI | AR2378, AR2387, AR2395, AR2396, AR2395, AR2295, AR2324, AR2325, AR2395, AR2395, AR2395, AR2395, AR2395, AR2995, AR39962, AR39962, AR39962, AR39962, AR39962, AR39962, AR39962, AR29962, AR39962, AR29962, AR39962, |         | AR292.6, AR221-4, AR235-3, AR176-3, AR266-3, AR2169-3, AR171-3, AR270-3, AR308-2, AR183-2, AR38-6, AR270-3, AR270-3, AR28-6, AR28-2, AR28-6, AR270-3, AR270-3, AR270-3, AR28-6, AR28-6, AR28-6, AR28-6, AR28-6, AR29-6, AR29-6 | AR060-7, AR055-7, AR185-6, AR313-6, AR218-5, AR300-5, AR240-5, AR089-4, AR282-4, AR299-4, AR283-4, AR090-3, AR096-3, AR104-3, AR104-3, AR219-2 H0170-1, S6026:1 and H0591:1. |         |         | MUZDTS, ZRI ISHI J. ARZHSI, LWISHS, ARLESS, ARLESS, ARLESS, ARLESS, ARZHS, ARZDSO, ARLESS, ARZDSO, ARRESS, ARR |
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                                                                                              | HLQDR48 | нгтнк66                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HLTIP94                                                                                                                                                                      | HLTIP94 | HLTIP94 | HLWAA17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| HLWBR05 763310 | 199   MEDGES, MERDES, ARRIPS, ARRIPS, ARCHS, SA, ARCHS, ARCHS, ARRIPS, ARRIPS, ARRIPS, ARLY ARRIPS, ARRIPS, ARRIPS, ARCHS, ARC |
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| HLWBK05        | 765310                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                | III.WBK05                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| 130 | HLWBY76 | 797609 | 140 | L0790-1, L0663-1, L0663-1, L0665-1, H0144-1, H0693-1, H0670-1, H0670-1, H0648-1, H0518-1, S0152-1, H0606-1, H044-1, H064-1, H0 |
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|     |         |        |     | 108061, LORGS1, LORGS1 |
| 131 | HLWCF0S | 460619 | 141 | ARI WORL, ARSS-9, AR2718, AR268, AR194, AR194, AR2755, AR2955, AR2656, AR2066, AR2066, AR1966, AR1966, AR2066, AR1966, AR2066, AR1966, AR2066, AR2064, |
| 132 | HLYAC95 | 778075 | 142 | ART649, AR18214, AR261:10, AR192-9, AR262-9, AR1918, AR2557, AR2967, AR231-7, AR201-6, AR232-6, AR2346, AR2366, AR296, AR2966, AR296, AR2966, AR296, AR2966, AR296, AR2967-5, AR291-5, AR291-5, AR2945, AR295-5, AR195-5, AR295-5, AR195-5, AR295-5, AR195-5, AR295-5, AR195-5, AR295-6, AR195-5, AR295-6, AR195-5, AR295-6, A |

| 1879-4, AR193-4, AR039-4, AR131-3, AR196-3, AR256-3, AR174-3, AR204-3, AR209-3, AR189-3, AR189-3, AR273-4, AR209-3, AR217-3, AR201-3, AR217-3, AR201-3, AR201-2, AR201-2, AR201-2, AR201-2, AR201-2, AR201-3, AR20 | RKIGHG, ARZDPG, ARZDSTG, RARZDSTG, ARRIDEG, RARIDEG, RARIDEG, RARIDEG, ARRIDEG, ARRI |         | AR2212, AR1617, AR2214, AR2244, AR1677, AR1687, AR2646, AR2456, AR1666, AR1097, AR16227, AR1617, AR1616, AR2616, AR261 | ARBO, |
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                                                                                              | HLYAN59 | HLYAP91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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|     |         |         |     | AR2D9-2, AR185-2, AR2D42, AR2G5-2, AR2G5-2, AR2G1-2, AR2G6-2, AR2G6-2, AR2D2-2, AR2D1-2, AR177-2, AR0G5-2, AR0G5-2, AR170-2, AR2G5-2, AR2G5-2, AR0G5-2, AR170-2, AR2G8-2, AR2G5-2, AR170-2, AR2G8-2, AR2G5-2, AR180-2, AR170-2, AR2G8-2, AR2G1-1, AR19-3, AR2G1-1, AR19-1, AR19-1, AR19-1, AR19-1, AR19-1, AR19-1, AR19-1, AR19-1, AR19-1, AR2G8-1, AR2G1-1, AR2G8-1, AR2G8 |
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| 136 | HMADK33 | 561941  | 146 | ADDRAS A ROBOS DA ARROSH AND SET, AND CHILD AND CHARLES, AND SETS, AND CHARLES, AND |
| 137 | HMADS41 | 596831  | 147 | APZP194, APZP194, ARRSSTA, ARR964S, ARR967A, RAR9194, ARRSP094, ARRSP09, ARRSSSP, AR |
| 138 | HMAMI15 | 1352406 | 148 | ARORGH4 AR28313, AROS510, AR2779, AR2829, AR1859, AR1049, AR30048, AR9068, AR3168, AR3998, AR2187, AR2197, AR2997, AR0997, AR3136, AR2306, AR0896, EBG242, S04521, S04421, S02781, S02781, B05861, LOO711, B00561, LOO711, B00561, B00511, LOO711, B00581, B00 |
|     | HMAM115 | 1049263 | 326 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 139 | HMCFY13 | 635301  | 149 | ARIT68, ARIG16, ARIG26, AR2666, ARIR16, AR2696, ARIG36, ARIT26, AR2285, AR2675, AR2335, ARD565, ARC865, AR2885, ARC865, AR2885, AR2884, ARIG56, AR295, AR274, AR1864, AR1864, AR1664, AR2174, AR21264, AR2794, AR21614, AR2174, AR21274, AR21274, AR2094, AR2994, AR2014, AR2994, AR2994, AR2994, AR2994, AR2994, AR2994, AR2994, AR29964, AR2994, AR2994, AR2994, AR29964, AR29964, AR29964, AR29874, AR2974, AR2974, AR29878, AR2984, AR29964, AR29884, AR2974, AR2978, AR2984, AR29884, AR298884, AR29884, AR298884, AR29884, AR298884, AR2988884, AR298884, AR29884, AR298884, AR2988884, AR298884, AR29884, AR298884, AR298884, AR298884, AR298884, AR298884, AR298884, AR29884, AR29884, AR29884, AR29884, AR29884, AR29884, AR29884, AR298884, AR2988884, AR298884, AR298884, AR298884, AR298884, AR298888884, AR298884, AR298884, AR29888884, AR29888884, AR29888884, AR |

| 141 | HMDAB56 HMEED18 | 560676 | 151 | MR2284, ARIP 31, ARI293, AR2233, AR2263, AR1293, AR2153, AR2263, AR2213, AR2061, AR2293, AR2021, AR2213, AR2233, AR2293, AR2033, AR2293, AR2034, AR2973, AR2034, AR297, AR2034, AR297, AR297, AR2902, AR297, AR2903, AR297, AR2903, AR297, AR2904, AR297, AR2904, AR297, AR2904, AR297, AR2904, AR297, AR2904, AR297, AR2904, AR297, A    |
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| 142 | HMEFT54         | 520307 | 152 | DUVALLI, DUVOLI, SARSALI, SARSOLI BIII INDOOS.1.<br>AROĞOT, AROSST, AROSSÇ, AROZSZ, Ç. AROZSZ, SARI 965.5, ARI 1965.5, ARI 1965.5 |

| AR2094, AR3194, AR394, AR3094, AR1819, AR2094, AR3164, AR3004, AR3704, AR3774, AR81834, AR2704, AR2704 | AR23516, ARI PREJ. ARTIFG 5, ANGEL 1, ANGEL 11, AR25711, ARGHL AR22516, AR19519, AR19619, AR2516, AR1999, AR2569, AR2996, AR296, AR296, AR296, AR1996, AR296, AR296, AR1996, AR2919, AR1906, AR1910, AR2912, AR1629, AR1629, AR1629, AR1629, AR1629, AR1629, AR1929, AR1629, AR1929, AR1629, AR1929, AR1929, AR1929, AR1929, AR2910, AR2912, AR1929, AR1929, AR2912, AR1929, AR2912, AR1929, AR2916, AR1929, AR2916, A | AR1695, AR2RES, AR1705, AR2252, AR2572, AR2242, AR3652, AR1712, AR2942, AR2171, AR3091,<br>AR1684, AR2611, AR1731, AR1631, AR2221, AR1781 |         |         |         | RR13111, ARROPA IL ARRONS, ARDIRS, ARTINGA, TARLOGA, ARZIOGA, ARRIOGA, ARRIOGA, ARRIOGA, ARRONG, ARRON |
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| ARROP-10. ARR559, ARROP7, ARR597, AR 1857, AR3137, AR3006, AR2186, AR31865, AR22405, ARL045, ARROP65, ARROP65, ARROP65, ARROP65, ARROP65, ARROP65, ARROP65, ARROP65, ARROP65, ARROP66, ARS964, AR2834, AR2773, AR2823, AR2192, L05605, L05454, 800022, L55742, H02401, 800461, H03331, L0591, L05441, 803741, H05201, S04541, S04061, and L38131, ARROP66, ARROP66 | AR2247, AR1897, AR296, KNIGSA, RIGGAS, ARIGGA, KRIGGA, ARIGGA, ARIGGA, AR22537, AR2717, AR2247, AR2714, AR12467, AR17464, AR1766, AR1766, AR1764, AR17 |         | REDISTA AREDA AL AREDA AR RITZEO, AREZEI RA AREDIO IG AREDO IS ARSOFIELA AREDO IDAGE AREDA |
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| AR2904, AR1092, AR1682, BASSO, ARR562, AR2652, AR262, AR1092, AR1616, AR2121, AR252, AR1062, AR1092, AR1092, AR291, AR2902, AR291, AR2902, AR291, | 163   AUGUSTA   AREASTIS, ARDREST, SARDEST, AREASTIS, | 164   MR2419, ARD946, ARD946, ARD87, ARB270, ARD870, ARD870, ARB57, ARB57, ARB56, ARD8715, ARB57, AR57, A | 1 165 ARIG420 AR05515, AR060F14, AR22913 AR38712, AR08911, AR31310, AR08910, AR3166, AR16168, AR16168, AR1617, AR2827, AR1647, AR1647, AR16467, AR18164, AR2794, AR2795, AR279 |
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| HRIST, ARZD26, ARGOZE, ARZD65, ARZD61, ARZD41, ARZD51, ARZD504, ARZD54, ARZD56, ARZD56, ARZD56, ARZD56, ARZD62, ARZD62 | MRZ216, ARZ353, ARZ643, AR1663, AR1703, AR2823, AR1722, AR2922, AR1972, AR2452, AR300, ARZ1172, AR1682, AR311, ARZ251, AR2911, AR1881, AR2961, AR2941, AR2941, AR2911, AR1881, AR3961, AR3911, AR1811, AR381, AR1711, S00522 | ARROBGO, ALSZEG, AROSEG, ARROSES, ARROSES, ARROSES, ARROBGS, ARROSES, ARROS | MR2217, AMD996, MR2215, MR3154, AN0964, ARR 1094, ARR543, ARR5464, ARR5146, ARR547, ARR544, ARR554, ARR555, ARR555, ARR595, AR | ARD99-IS ARD33-14, ARIGE14, ARIGE14, ARIGE31, ARIGE12, ARIGE11, ARIGE11, ARD96-10, ARITR94, ARIZP94, AR2998, AR2998, AR3998, AR2946, AR295-17, AR395-17, AR390, AR395-17, AR396, AR295-17, AR396, AR295-18, AR295-18 |
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| 164 | HNHFM14 | 664507 | 174 | MARZPOSA, ARMSTATI, AMUSETI, ARMSET, ARMSONE, ARMSONE, ARSONE, ARSONE, ARMSTATA, ARMSONE, ARMSTATA, ARMSONE, ARMSTATA, ARMSONE, A |
| 165 | HNHFR04 | 646709 | 175 | AR2163, AR1763, AR2282, AR1682, AR3992, AR1692, AR2132, AR2712, AR2712, AR1712, AR1992,<br>AR2362, AR2962, AR272, AR2242, AR2742, AR1651, AR2631, AR1661, AR2881, AR1631, AR2871,<br>AR1621, AR2041, S0053, AR364, AR2742, AR1654, AR2631, AR1661, AR2881, AR1631, AR2871,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 166 | HNHNB29 | 895462 | 176 | MARIBERS, ARRIGZO, MRIGERO, MRIGERO MRIPER, ARRESTO, ARRESTO, ARRIGER, ARRIGER, MAZSEL, MRIPER, ARRIGER, MAZZEL, MRIGERO, MRICERO, MRIPER, ARRIGER, MRIPER, MRIPER, ARRIGER, MAZZELI, ARCHERO, MAZZELI, ARCHERO, ARRIGERO, ARRIGERO, MRIPERO, ARCHERO, ARCHERO, ARCHERO, ARCHERO, ARRIGERO, ARRIGERO, MRIPEROS, ARCHERO, ARCHERO, ARRICER, ARCHERO, ARCHERO, ARRIGERO, ARRIGERO, MRIPEROS, ARCHERO, ARCHERO, ARRICER, ARCHERO, ARCHERO, ARRIGER, ARRIGER, MRIPEROS, ARCHERO, ARRICER, ARRIGER, ARCHERO, ARCHERO, ARCHERO, MRIPERO, ARCHERO, ARRICER, ARRIGER, ARCHERO, ARCHERO, ARCHERO, MRIPEROS, ARCHERO, ARCHERO, ARRIGER, ARCHERO, ARCHERO, ARCHERO, MRIPEROS, ARCHERO, ARCHERO, ARCHERO, ARCHERO, ARCHERO, ARCHERO, ARCHERO, MRIPEROS, ARCHERO, ARCH |
| 167 | HNHOD46 | 843488 | 177 | AR09922, AR1913-28, AR09621, AR0891, AR29916, AR18271, AR21711, AR31611, AR30010, AR10410, AR0699, AR2198, AR2138, AR34047, AR1654, AR1626, AR1754, AR2182, AR3184, AR2185, AR3475, AR3185, AR375, AR3185, AR375, AR3764, AR3764, AR3764, AR3764, AR3764, AR3774, AR3764, AR37 |

| NR1794, NR284, NR284, NR1784, ARN (44, RN9294, RR394), ARSZ-4, NR2864, ARSZ-6, ARSZ-8, | ARIDE'S ARIZHES, ARUSES, AROZESIG, KRIGHES, ARDGESTIS, ARIZHES, MAZZHIS, ARIZHES, AR |         |         | AR2186, AR2405, AR282,5 AR275, AR3165, AR0964, AR2194, AR1854, AR1044, AR3003, AR2993, AR0963, AR398, AR398, AR398, AR398, AR095, AR383, AR095, AR393, AR095, AR095, AR095, L0663, L0663, AR38, AR095, L0804, L0904, L0791, L0664, L0664, L0665, L0665, L0665, L0665, L0777, L0747, L0749, L0777, L0779, L0777, L0779, AR097, AR0979, AR0979, AR0977, L0777, L0779, AR0979, AR0979, AR0977, L0779, AR0977, AR0979, AR0979, AR0977, AR0979, AR0977, AR0979, AR0977, AR0979, AR0977, AR0979, AR0977, AR0979, AR0977, AR0979, AR0979, AR0977, AR0979, AR0977, AR0979, AR0 | RD917, KR1645, ARD955, ARD965, ARD585, AR1665, ART1704, ARD974, ARD9894, ARD694, ARD864, ARD864, ARD864, ARD864, ARD864, ARD864, ARD864, ARD864, ARD8694, ARD604, ARD864, ARD864, ARD864, ARD864, ARD865, ARD869, ARD866, ARD8664, ARD8664, ARD8663, ARD8669, ARD8664, ARD86644, ARD866444, ARD8664444, ARD86644444, ARD8664444, ARD86644444, ARD866444444, ARD866444444, ARD8664444444, ARD8664444444, ARD86644444444, ARD86644444444444444444444444444444444444 |
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| MR247, ARBIG, ARBOA, ARBOA, ARRILA, ARBOA, A |         |         | ARZDYIA, ARKSGI, Z. MRUH, ARKIJI, M. MRUH, ARKUNGA, ARKUN |
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| IHNTYNII   6998-8   33   ARZ7712, ARZ3812, AR10-10, AR079-8, AR10-8, AR216-8, AR20-8, AR216-8, AR20-7, AR20-9, AR10-6, AR20-4, AR10-6, AR20-7, AR20-   |     |         |         |     | H0485:1, H0013:1, L0564:1, L0770:1, L0794:1, L0809:1, H0519:1, S0378:1, L0756:1, L0777:1 and H0667:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| HNTSV18 1041383 183 HNTSV18 887940 337 HOCNF19 835049 184 HODDF13 684307 185 HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |     | HNTNI01 | 699848  | 336 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HOCNF19 839049 184 HODDF13 684307 185 HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 173 | HNTSY18 | 1041383 | 183 | AR277:12, AR283-12, AR104-10, AR039-8, AR055-8, AR089-8, AR218-8, AR096-8, AR316-8, AR282-7, AR299-7, AR096-8, AR296-6, AR096-6,     |
| HOCNF19 835049 184 HODDF13 684307 185 HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |         |         |     | MK102.4, AK103.4, AK122.4, AK193.4, AK103.4, AK104.4, AK100.4, AK100.4, AK111.4, AK101.1, AK222.4, AK221.4, AK243.3, AR212.3, AR240.3, AR217.3, AR300.3, AR168.3, AR264.3, AR205.3, AR311.3, AR263.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| HOCNE19 835049 184 HODDE13 684307 185 HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |         |         |     | AK258:1, AK1 /3:1, AK297:1, AK1 /3:1, AK1 /8:1, AK296:1, AK262:1, AK289:1, AK268:1, AK237:1 L0805:2, H0619:1, H0547:1 and S0190:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HOCNF19 R35049 184 HODDF13 684307 185 HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     | HNTSY18 | 897950  | 337 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 174 | HOCNF19 | 835049  | 184 | AR243:5, AR213:4, AR217:4, AR096:4, AR253:3, AR204:3, AR308:3, AR205:3, AR272:3, AR197:3, AR039:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR312.3, AR195.3, AR053.3, AR162.3, AR282.3, AR215.2, AR218.2, AR238.2, AR171.2, AR311.2, AR201.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDF13 684307 185<br>HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |         |         |     | AKZONIC, ARIONIC, ARANONIC, AKZOTIC, AKZOTIC, AKZOTIC, AKZOTIC, AKZOTIC, AKZOTIC, ARANONIC, AKTOTIC, AKTOTIC, AKZOTIC, A    |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | MKI 86.2, MKI 96.2, MKI 89.2, MKI 84.2, MKZ 86.2, MKZ 9.2, MKI 82.2, MKZ 91.2, MKO 93.2, MKZ 47.2, MKI 04.2,<br>  MRO 89-3   MRO 97-3   MRO 81-1   MRI 83-1   MR 98-1   M |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR191:1, AR270:1, AR178:1, AR299:1, AR293:1, AR239:1, AR296:1, AR193:1, AR060:1, AR257:1, AR225:1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDF13 664307 185 HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     |         |         |     | AR258:1, AR246:1, AR180:1, AR268:1 S0442:2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 175 | HODDF13 | 684307  | 185 | AR312:21, AR308:20, AR205:19, AR253:19, AR250:19, AR309:19, AR264:18, AR311:16, AR212:16, AR213:15,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR218:14, AR096:14, AR272:14, AR313:14, AR263:14, AR161:13, AR162:13, AR163:13, AR165:13, AR164:12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR175:12, AR053:12, AR219:12, AR089:12, AR166:12, AR246:12, AR178:11, AR270:11, AR254:11, AR271:11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR173:11, AR274:10, AR039:10, AR192:10, AR174:10, AR176:10, AR216:10, AR189:10, AR193:10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR183:9, AR221:9, AR268:9, AR191:9, AR252:9, AR210:9, AR245:9, AR172:9, AR269:9, AR290:9, AR197:9,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AKIOUS, AKZ42.8, AKZ17.8, AKZ24.8, AKIOS.3, AKZ10.8, AKZ10.8, AKZ10.8, AKZ08.8, AK179.9, AK179.8, AXZ08.8, AXZ0    |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | JAKE 1777. AR199: 6. AR170: 6. AR295: 6. AR291: 6. AR188: 6. AR198: 6. AR243: 6. AR245: 6. AR275: 6.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR104:6, AR299:6, AR204:6, AR229:5, AR300:5, AR237:5, AR294:5, AR169:5, AR285:5, AR225:5, AR033:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR296:5, AR286:5, AR287:5, AR261:5, AR238:5, AR168:5, AR289:4, AR231:4, AR230:4, AR223:4, AR277:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR214:4, AR226:4, AR228:4, AR203:4, AR239:4, AR196:4, AR255:4, AR234:4, AR235:4, AR235:4, AR262:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDN92 422913 186                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |         |         |     | AR260:3, AR236:3, AR257:3, AR061:3, AR256:3, AR232:3, AR200:3, AR227:3, AR258:3, AR283:3, AR055:2,<br>AR207:2-H0328:1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| ARCHES, ARCHES | 176 | HODDN92 | 422913  | 186 | AR161:4, AR162:4, AR163:4, AR192:4, AR165:4, AR308:4, AR264:4, AR176:4, AR311:3, AR164:3, AR309:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AR224-2, AR173-2, AR060-2, AR288-2, AR282-2, AR285-2, AR271-2, AR185-2, AR175-2, AR039-2, AR275; AR275; AR275;                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |     |         |         |     | AR166:3, AR312:3, AR213:3, AR214:3, AR193:3, AR225:3, AR313:3, AR096:3, AR089:3, AR2/10:3, AR172:3,  <br> AR235:3, AR299:2, AR201:2, AR201:2, AR104:2, AR269:2, AR195:2, AR294:2, AR169:2, AR215:2, AR290:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |     |         |         |     | AR224.2, AR173.2, AR060.2, AR288.2, AR288.2, AR285.2, AR271.2, AR185.2, AR175.2, AR039.2, AR275.2, AR274.3, AR2    |

| HODEJS2 RIOPNQ33 RIOPNQ33 RIOPNQ33 | 835027<br>1184465<br>919896<br>906694                           | 188 | HIGHST, IQ. HORSAS, SULIS, LONGAS, HORSAS, HORSAS, HORSAS, HORSAS, HORSAS, HORSAS, HORSAS, HORSAS, LONGAS, HORSAS, HOR |
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| HOFMQ33                            | 902639                                                          | 340 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HOFMQ33                            | 702186                                                          | 341 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HOHBY44                            | 873264                                                          | 189 | /AR205:3, AR169:3, AR216:2, AR245:2, AR171:2, AR282:2, AR213:2, AR172:2, AR163:2, AR236:2, AR246:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                    | HOPNQ33 HOPNQ33 HOPNQ33 HOPNQ33 HOPNQ33 HOPNQ33 HOPNQ33 HOPNQ33 |     | 1184465 188<br>19896 338<br>906694 339<br>90759 340<br>702186 341<br>87264 189                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| 180 | HOHBY44 HOQBI82 HQQBI82 HQQBI82 HQQBI82 HQQBI82 | 873265<br>1352366<br>1352366<br>888338<br>887453<br>589431 | 345<br>344<br>1910<br>1910 | ARRIG-2, ARSSE, ARGSE, ARGSE, ARSSE, ARB, ARSSE, ARB, G., ARB) 2, ARSDE, ARB, B., ARSSE, ARB, ARRIG-2, ARSDE, ARGSE, ARGS |
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|     |                                                 |                                                            |                            | AR2162, AR2282, AR3122, AR2152, AR1822, AR1862, AR3162, AR3162, AR3032, AR362, AR3162, AR3042, AR3042, AR3042, AR3062, |

| AR127-15, AR267-14, AR251-14, AR261-14, AR261-11, AR201-1, AR1061, AR1061-1, AR201-10, | _ 9     | A RUEZI Z. ARZPOS, ARTERIO, ARZPO, ARZPOS, ARGOS, ARGOS, ARGOS, ARZPOS, ARZPOS |
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| 854234                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 566845  | 429229                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| HOSD125                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HOSDJ25 | HOUCQ17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 182                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         | 183                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |         |     | 80196:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| 184 | HPEAD79 | 520202  | 194 | MAZDTSA, ANDESA, ANDESA, ANDESA, ANDESA, ANDESA, SANDESA, ANDESA, ANDE |
| 185 | HPIBOL5 | 1310868 | 195 | MAZD4010, AR1796, MAZP08, AR2219, AR221957, AR1612, AR1612, AR1612, AR1617, AR1820, AR181637, AR22856, AR19160, AR1796, AR2786, AR1816, AR1816, AR1816, AR1816, AR2786, AR1816, AR1816 |
|     | HPIBO15 | 590741  | 347 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 186 | НРЈВІЗЗ | 669589  | 196 | MRICHI-LA MICCLA MICHILLA MISHS & MICKS ARDNAS ARCHES ARDNOS ARAZHISA, ARZDS A |
| 187 | HPJBK12 | 1011467 | 197 | AR2155, AR1974, AR0394, AR3094, AR2454, AR1613, AR1623, AR1633, AR2043, AR1653, AR2553,<br>AR1693, AR2643, AR2823, AR2723, AR07853, AR1803, AR2133, AR1723, AR2532, AR1662, AR2122,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| AR2D_CA AR222_AR277_AR286_AR26_AR26_AR26_AR26_AR26_AR26_AR26_AR66_AR26_AR2 | 1077-51, 1076-11, 1076-11, 1076-11, 1079-11, 1076-11, 1075-11, 1076-11, 1071-11, 075-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076-11, 1076 |
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| L0761:1, L07<br>H0555:1, L07                                               | L0761:1, L0772:1, L0648:1, L0803:1, L0650:1, L0805:1, L0809:1, L0647:1, L0665:1, H0539:1, H0521:1, H0696:1,<br>H0555:1, L0754:1, L0749:1, L0753:1, L0755:1, L0757:1, L0605:1, L0599:1 and L3352:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|         | ARMOSTO, ARIDATO, ARMOSTZ, ARMOSTA, RANDSGA, RANDSGA, ARMOSTA, ARMOSTO, ARMOSTO, ARMOSTA, ARM |         | ARR 1931, ARR 511, ARR 611, ARR 610, ARR 610, ARR 624, ARR 623, ARR 623, ARR 624, ARR 625, AR |         | MR22251, MR2131, MR2132, MR22530, MR17214, AR1719, AR1719, AR1719, AR1859, AR2159, AR2149, AR1858, AR2168, AR168, AR168, AR168, AR168, AR268, AR1710, AR168, AR1710, AR168, AR1710, AR168, AR1710, AR169, AR1710, AR169, AR1710, AR169, AR1710, AR169, AR1710, AR169, AR1710, AR169, AR1710, A |
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| MARZEA, ARRISEL, MROBEL, MASCISI, MASCIA, MASC |         |         | AR052:15 AR213:14 AR053:10 AR244:8 AR096.7 AR184:6 AR215:6 AR310:5 AR251:5 AR241:5 AR221:4 | RR2154, AR1704, AR2701, AR2061, RR209, AR1863, AR2643, AR31231, RR2095, AR32923, AR1863, AR8093, AR8094, AR8064, AR8066, AR8064, AR806 | ARNS I, ARDS-A. ARZOEL, ARZY-I, ARZZI, ARZYI, ARZYI, ARNON, ARD ARRON, ARNON, ARD ARZOLI, AND ZI,<br>ARZUDI, ARZOSI, ARRISI, ARIGEL, ARZER, ARZOLI, ARZSTI, ARD GEL, ARD GEL, ARD GEL, ARD GEL, ARZOLI, ARZOLI, ARZOLI, ARZOLI, ARZOLI, ARZOLI, ARD GEL, LOTAGLZ, |         |         |         | AR0558, AR060-6, AR218-6, AR310-5, AR316-4, AR089-4, AR2040-4, AR282.3, AR185-3, AR10453, AR209-3, AR209-2, AR219-2, AR219-2, TR318-4, AR09-5, AR209-2, AR219-2, AR219-2, AR209-2, AR20 |         |         | MURGOS, ARRIGIZ ARRIGIZ PARGELL ARBISTIL ARZUSA, ARRGSA, ARRIGSA, ARRIGSA, ARRIGSA, ARROROSA, ARRIGSZA, ARRIGZA, ARRIGZA |
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| NR2864, NR215A, NR215A, NR2964, AR2364, AR2375, AR1069, AR2665, ARR216A, AR215A, AR1093, AR2264, AR2669, AR2663, AR2363, AR216A, AR216 | MK0993, AR13132, AR0962, AK0892, AK0891, AK08161, AR1614, AR1811, AK1811, AK1611, AR1611, AR16 |         | NR29045, AR2015, ARTARSATA, ARBOTZ, ARESPIGA, RAZPAH, ARSH-QI, ARRISTIO, ARRISTIO, ARRISTS, ARABOTS, ARBOTS, A |         | MR23-62, AR26-64-9 AR29-09    MR16-19, MR16-29, AR18-66, MR16-66, AR18-66, AR18-05, AR19-05, AR18-05, AR19-05, AR29-05, AR29-05 |
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| MRIPS, AREZES, |         | ARZOGIS, ARSUGIS, ARZOGIO, ARZOGIS, ARGHER, KAROGIS, ARZOGIS, ARBIGIST, ARZOGIS, ARZ | AR01619, AR0554, AR27713, GAT209-22, AR104-31, AR089-39, AR2852, AR1059-25, AR059-25, AR059-24, AR259, AR27713, CAR209-14, AR21610, AR21810, AR219-3, AR259, | AR060:10, AR089:9, AR055:7, AR104:7, AR313:5, AR039:4, AR218:4, AR184:4, AR316:4, AR096:4, |
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|     | CONTRACTOR         |         |     | MR IRS4, ACR213, AUSD43, AUSD43, AURISA ARCH214, AURISA, AURIS |
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| 203 | HSDSB09<br>HSHAX21 | 463645  | 213 | AR2264, LAR3D98, AR2358, AR2308, AR2528, AR2347, AR3087, AR2567, AR1727, AR2717, AR1627, AR2716, AR2716, AR1956, AR1956, AR295, AR1956, AR295, |
| 204 | HSID181            | 589447  | 214 | ARBEISHA, ARROBGAS, ARROBGAS, ARTITASA, RANSOLT, ARRISON, ARROBO, ARRISON, ARROBGAS, RANGES, RARGELS, RARGES, RARG |
| 205 | HSJBQ79            | 1304677 | 215 | HARDESTO, MORGO, ARADOR, ARAZERS, ARADOR, ARABE, ARRS, ARRSS, ARRSS, ARADOS, ARDOR, ARDOS, ARDOR, ARADOS, ARADOR, ARAD |

|     |         |         |     | [105441, 105461, 100861, 102861, 106281, 1.06541, 1.05651, 106891, 106701, 106601, S00371, S00281, S00321, L05951, 106681, 106681, 106671, S01921, S01921, and S04241.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|     | HSJBQ79 | 869199  | 369 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     | 6/Oarsh | 371784  | 370 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 206 | HSKDA27 | 1352409 | 216 | MR099106, ARTOR 103, ARDS-101, ARDS-101, ARDS-101, ARDS-103, ARDS- |
|     | HSKDA27 | 1074734 | 371 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     | HSKDA27 | 872570  | 372 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 207 | HSKGN81 | 676075  | 217 | MRST530, RATEST-90, ARZEST-92, RARZEST-91 STAREST-91 (REI-BIA, RREST-91), ARZEST-91, ARXEST-91, ARZEST-91, ARZ |

| 104561, 102501, 70071, 105811, 100521, 100451, 100541, 100561, 1002041, 100831, 100541, 100831, 100541, 100831, 100541, 100831, 100541, 100831, 100541, 100831, 100541, 100831, 100541, 100831, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531, 100531 |         | AR2235, AR2215, AR2152, AR2172, AR2822, AR2862, AR28621, AR3881, AR2861, L05668, L05668, L05684, L05695, L04854, S00033, L07483, L07313, S03762, S03602, L04852, L04882, L057512, L057512, L05751, L05561, L05561, L05691, L05991, L05 | ARIOG, ARIOGA, ARIBGA, ARBIGA, AREPLE, ARIPES, AREPLE, AREPLES, ARBOES, ARESOE, ARESOES, ARES | MR2428, AR2085, AR2386, AR1706, AR2075, AR20154, AR2163, AR2063, AR2063, AR172, AR2082, AR1822, AR1822, AR20873, AR1822, AR20873, AR1822, AR20873, AR1822, AR20873, AR1822, AR20873, AR |         | AR1976, AR2718, AR1976, AR1677, AR1971, AR3017, AR10876, AR2346, AR2314, SAR2956, AR2346, AR23296, AR18246, AR1976, AR18736, AR187374, AR2374, | AR224, AR304, AR004, AR004, AR RUSS, AR WOSS, AR RUSS, AR234, AR235, AR235, AR235, AR235, AR235, AR235, AR335, AR335, AR335, AR335, AR335, AR336, AR3 |
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| ARI WSG A RAZDE, A RAZDE, A RAZDES, A RADIG, A RADES, A RADES, A RAZDE, A R | RR215-6, ARR93-, ARR64-, ARR94-, AR994-, AR994-, ARR94-, ARR95-, ARR94-, ARR95-, AR819-3, AR213-, AR819-3, AR81 | MR1391, ARD993, ART390, AR06916, MR08915, AR28016, AR29914, ARAPO914, ARR (1511) ARR (1512) ARR (15 |
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| <ul> <li>HOSPILL HOSSIL, HORGEL, HONDEZL, HOSPILL HOSPILL HOSPILL DESPLICATION LEGISL LORGEL LOTORIL,</li> <li>LOWSEL, LOWGILL LORGEL, LOTORIL, LOTORIL, LOTORIL, LOTORIL, LORGEL, LOR</li></ul> | 226 NEZ 1622, SEZ REJELJ9, KNØGER, KARTIZIT, ARZIZIT, ARZZZIT, ARZZZZIT, ARZZZZIT, ARZZZZIT, ARZZZZIT, ARZZZZIT, ARZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZ | 375     | 227 AR216-62 AR214-45 AR205-64, AR215-58, AR1695-8, AR210-73, AR217-73, AR217-73, AR217-73, AR217-73, AR217-73, AR217-73, AR217-73, AR217-73, AR217-74, AR217-73, AR217-74, AR21 |
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                                                 | HSYAZ63                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HSYAZ63 | HSYBG37     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|     | HSYBG37 | 581098  | 376        | RATEOSISTA ARSESTI A ARSESTI ZA RASTI A RASESI, ZA ARSESTI ZA RASESTI A RASESTI A RASESTI ZA RASETI ZA RASESTI ZA RASETI ZA RASESTI ZA RASETI ZA RASESTI ZA RASESTI ZA RASETI ZA RASESTI ZA RASETI ZA R |
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| 218 | HTADWOL | 844835  | 528<br>278 | AREL REL AREL FOL ARCRETO, ARCHES, ARCHES, ARELS, A |
| 219 | HTAEE28 | 1018291 | 229        | AR1705, AR1694, AR2213, AR2963, AR2173, AR2422, AR2662, AR1712, AR1952, AR2452, AR20112, AR7722, AR182, AR3002, AR2161, AR2671, AR3961, AR2741, AR1881, AR2161, AR2181, AR2181, AR2181, AR2181, AR2181, AR281, AR381, AR381 |
|     | HTABE28 | 882919  | 377        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 220 | HTDAF28 | 396835  | 230        | ARZI419, ARZB319, ARZB317, ARZB317, ARZB217, ARBD716, ARB1116, ARTD015, AR16815, AR16915, ARZB414, ARZB414, ARZB114, ARZB114, ARZB114, ARZB114, ARZB114, ARZB114, ARZB114, ARZB114, ARZB114, ARZB116, ARBB41, ARZB110, ARBB41, ARZB110, ARBB41, ARZB110, ARBB41, ARZB410, ARBB410, ARBB410 |

| AR2106, AR2736, AR0049, AR8096, AR2052, AR2052, AR2052, AR2052, AR2058, AR21676, AR2058, AR21676, AR2056, AR2056, AR2056, AR2056, AR2056, AR2066, AR2067, AR20 | AMENGA, AND HAZHA, AND HROA, AND HAZHA, HAND HAZHA, AND HAZHA, AND HAZHA, HADSH, LOOSH, LOO |         |         | ARI 74-12, ARI 91-12, ARI 90-11, AR244-11, ARI 81-11, AR391-10, ARI 86-10, ARI 189-10, ARI 15-10, ARI 195-10, ARI 895, ARI 196-2, AR2949, AR ARS99, ARI 194-2, ARI 195-20, ARI 195-3, ARS68-3, ARI 818-3, ARZ736, AR2746, AR16-34, AR14-7, ARI 195-7, ARI 195-7, ARI 165-7, ARI 195-7, ARI 195-6, ARI 195-7, ARI 195 |
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| HTXKF95 891275 248 HTXKF95 834438 389 HTXON32 838288 249                                                                             |   | HTXJM03 | 603918 | 247 | MR2B131, ARZEZIO, MR2B28, ARB127, ARB767, ARB066, ARSE46, ARSE46, ARRE166, ARRE166, ARZE46, ARZE56, ARZE516, ARZE516, ARZE516, ARRE56, ARB167, ARB066, ARZE46, ARZE56, |
| HTXKF95 834438 389<br>HTXON32 838288 249                                                                                             |   | ITXKF95 | 891275 | 248 | MR2666, ARDEGA, KNITSA, ARREGA, RIREGA, KRIEGA, KNESEA, KNESEA, KRUGGA, ARRIGA, ARROGA, ARRIGA, ARROGA, ARRIGA, ARROGA, ARRIGA, ARROGA, ARRIGA, ARDEGA, ARROGA, ARRIGA, ARDEGA, ARROGA, ARRIGA, ARDEGA, ARROGA, ARROGA, ARROGA, ARROGA, ARROGA, ARROGA, ARROGA, ARDEGA, ARROGA, ARDEGA, ARROGA, ARDEGA, ARROGA, ARROGA |
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| AR035.38, AR255.57, AR296.37, AR210.36, AR190.36, AR257.36, AR28<br>AR218.34, AR163.32, AR247.32, AR176.31, AR180.30, AR312.30, AR25 |   | HTXON32 | 838288 | 249 | AR195-107, AR197-91, AR172-81, AR246-73, AR295-74, AR227-75, AR218-667, AR232-64, AR235-67, AR119-66, AR1995-66, AR291-63, AR222-54, AR19-63, AR291-64, AR297-94, AR297-94, AR296-74, AR296-74, AR179-64, AR296-74, AR29 |

| HUVEB53 571200 HUVAAD63 838626 | MRIGOZO, ARRESE O, ARRESE O, ARRESE O, ARRESE SE ARRESE ARREST | 250 M2779, ARDD9, ARD157, ART 1927, ART 1956, ART 2556, | 251   ANDS3-A KRIT-3. ARE342, AR RNG-2, ARGO-2, ANDSO-2, ARGES-1, ARGO-2, ARGES-1, ARGO-3, ARG | 222 AUG617, AR17314 AR16114, AR16214, AR172114, AR16214, AR16314, AR18151, AR181514, AR16617, AR16717, |
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| c; c |         |        |     | AR315:2, AR256:2, AR2442, AR259:2, AR205:2, AR246:2, AR061:1, AR184:1, AR284:1, AR280:1, AR283:1, AR055:1 H0441:1, H0581:1 and H0604:1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| 070  | HWAAD63 | 833089 | 390 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 070  | HWAAD63 | 793875 | 391 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 543  | HWADJ89 | 905662 | 253 | AR252:29, AR250:29, AR253:21, AR254:10, AR282:6, AR215:6, AR164:5, AR164:5, AR166:5, AR089:5, AR161:5,<br>AR246:5, AR162:5, AR271:5, AR240:5, AR163:5, AR163:5, AR263:4, AR243:4, AR274:4, AR195:4, AR205:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|      |         |        |     | AR313:4, AR096:4, AR299:4, AR180:4, AR213:4, AR193:4, AR214:4, AR169:4, AR300:4, AR311:4, AR264:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR192:4, AR173:4, AR207:4, AR312:3, AR285:3, AR171:3, AR309:3, AR060:3, AR275:3, AR308:3, AR196:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR272:3, AR316:3, AR269:3, AR257:3, AR261:3, AR170:3, AR270:3, AR183:3, AR242:3, AR245:3, AR296:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR199:3, AR287:3, AR295:3, AR175:3, AR033:3, AR172:3, AR2222:2, AR188:2, AR039:2, AR185:2, AR290:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR286.2, AR247.2, AR238.2, AR191.2, AR297.2, AR178.2, AR268.2, AR291.2, AR262.2, AR200.2, AR235.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR1042, AR2832, AR2122, AR2102, AR2882, AR2032, AR2012, AR1742, AR2772, AR1972,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|      |         |        |     | AR1882, AR2582, AR2942, AR2982, AR29822, AR2882, AR2182, AR218 |
|      |         |        |     | AK1902, AK239;2, AK228;2, AK227;2, AK233;2, AK234;1, AK177;1, AK231;1, AK179;1, AK061;1, AK266;1,<br> AK055;1, AR226;1, AR219;1, AR289;1, AR232;1, 110581;1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 244  | HWBCP79 | 846382 | 254 | AR313:44, AR039:36, AR196:28, AR089:27, AR096:25, AR299:23, AR300:21, AR185:18, AR163:17, AR161:17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR162:17 AR240:16 AR277:15 AR164:15 AR218:15 AR173:14 AR316:14 AR165:14 AR229:13 AR199:13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|      |         |        |     | AR247:12 AR060:12 AR175:12 AR234:11 AR174:11 AR264:11 AR179:11 AR195:10 AR191:10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|      |         |        |     | AR192:10, AR238:9, AR193:9, AR219:9, AR242:9, AR178:9, AR293:9, AR104:9, AR180:9, AR262:9, AR275:9,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR177:9, AR166:8, AR181:8, AR200:8, AR257:8, AR053:8, AR188:8, AR236:8, AR282:8, AR233:8, AR271:8,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR296:7, AR312:7, AR203:7, AR226:7, AR183:7, AR285:7, AR197:7, AR182:7, AR230:7, AR269:7, AR274:7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR235:7, AR204:6, AR231:6, AR189:6, AR212:6, AR297:6, AR237:6, AR213:6, AR295:6, AR198:6, AR245:6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR286:6, AR287:6, AR228:5, AR263:5, AR270:5, AR055:5, AR272:5, AR176:5, AR260:5, AR294:5, AR308:5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR261:5, AR239:5, AR268:5, AR309:5, AR033:5, AR290:4, AR201:4, AR227:4, AR256:4, AR288:4, AR250:4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR25554, AR190:4, AR283:4, AR291:4, AR243:3, AR211:3, AR205:3, AR210:3, AR267:3, AR246:3, AR215:3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      |         |        |     | AR311:3, AR207:3, AR225:3, AR224:3, AR289:2, AR232:2, AR168:2, AR223:2, AR214:2, AR266:2, AR222:2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|      | HWBCP79 | 646977 | 392 | ARLULE, ARESTE, ARUZEL, AROULT 100300.1 and 10103.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 245  | HWBEM18 | 949402 | 255 | AR225:61, AR169:56, AR223:52, AR170:52, AR168:45, AR215:41, AR171:40, AR214:37, AR243:34, AR296:34,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR254:32, AR266:31, AR222:27, AR291:26, AR246:26, AR224:25, AR289:23, AR172:23, AR221:22, AR297:21,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR253:20, AR216:20, AR217:20, AR245:19, AR213:18, AR183:18, AR250:18, AR288:17, AR205:16, AR179:16,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR295:16, AR283:15, AR270:15, AR039:15, AR256:15, AR193:15, AR255:14, AR269:14, AR178:14, AR285:13,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR096:13, AR197:13, AR271:13, AR235:13, AR261:12, AR316:12, AR195:12, AR242:12, AR180:12, AR268:11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR260:11, AR192:11, AR176:11, AR175:11, AR089:11, AR267:11, AR181:10, AR212:10, AR173:10, AR293:10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|      |         |        |     | AR1823, AR1633, AR2623, AR1613, AR1623, AR2873, AR2403, AR2013, AR1653, AR247,8, AR1643, AD204,8, AD20 |
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| MR 1995, ARN 24585, ARSSES, ARSSEY, ARTHS4, ARSSES, ARSSES, ARRSES, ARRSES, ARRSTS4, ARRSES, ARRSTS4, ARRSES, ARRSTS4, ARRSES, ARRSES, ARRSTS4, ARRSES, ARRSES |         |         | ARITIS, ARBORA, ARZTIZ, ARSP22, ARZDS, ARDS, ARSZA, ARSTIZ, ARSTZ, ARDS, ARDS, ARZDS, ARDS, ARDS | AR2SH1 A RUBON B, AR316, (A AR22), G. RROBOL J. AR217, A RUDOL J. AR202, A AR204, A AR2412, AR2111, AR2041, AR20511, AR05511, AR006, 10, AR2094, AR2065, AR21089, AR21089, AR2118, AR2115, AR2016, AR2 | ARIGGS, ARIGIGS, AREGS, AR2216, AR2095, AR2724, AR2634, AR8534, AR2534, AR2534, AR2534, AR2634, AR1694, AR1694, AR1694, AR1694, AR1694, AR1694, AR1694, AR1694, AR1694, AR2695, AR2695 |
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| AR262-2, AR190-2, AR190-2, AR172-2, AR291-2, AR291-2, AR291-2, AR180-2, AR291-3, AR171-1<br>IAR10-4, AR09-61, AR20-41, AR28-41, AR26-61, AR29-61, AR29 | AR223:2, AR189:2, AR201:2, AR267:1, AR171:1,                     | AR300:1, AR250:1, AR199:1, AR033:1 L0439:4,                      | 47:1 and H0352:1.                                                    |
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| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | AR262:2, AR190:2, AR172:2, AR312:2, AR227:2, AR291:2, AR223:2, A | AR104:1, AR296:1, AR294:1, AR294:1, AR258:1, AR246:1, AR300:1, A | L0748:2, H0351:1, S0364:1, L0768:1, L0550:1, L0375:1, L0747:1 and H0 |

10088] Table IC summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID), contig sequences (contig identifier (Contig ID); contig mucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon Fronto", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereo).

Table 1C

| cDNA Clone | SEQ ID NO:X | CONTIG ID: | BAC ID: A | SEQ ID NO:B | EXON        |
|------------|-------------|------------|-----------|-------------|-------------|
| ID         |             |            |           |             | From-To     |
| HAUAI83    | 30          | 639009     | AC010422  | 781         | 1-326       |
|            |             |            |           |             | 1552-2084   |
|            |             |            |           |             | 2162-2261   |
|            |             |            |           |             | 2300-2427   |
|            |             |            |           |             | 4485-5868   |
|            |             |            |           |             | 5948-6362   |
|            |             |            |           |             | 7914-8017   |
|            |             |            |           |             | 8569-8681   |
|            |             |            |           |             | 8765-8875   |
|            |             |            |           |             | 8968-9037   |
|            |             |            |           |             | 9284-9499   |
|            |             |            |           |             | 9742-9910   |
|            |             |            |           |             | 10837-11187 |
|            |             |            |           |             | 11271-11321 |
|            |             |            |           |             | 11554-11707 |
|            |             |            |           |             | 11783-12766 |
|            |             |            |           |             | 12866-13225 |
|            |             |            |           |             | 13256-13827 |
|            |             |            |           |             | 14284-14367 |
|            |             |            |           |             | 14890-15090 |
| HAUAI83    | 30          | 639009     | AC018761  | 782         | 1-326       |
|            |             |            |           |             | 1176-1284   |
|            |             |            |           |             | 1552-2084   |
|            |             |            |           |             | 2162-2261   |
|            |             |            |           |             | 2300-2426   |
|            |             |            |           |             | 4485-5868   |
|            |             |            |           |             | 5948-6362   |
|            |             |            |           |             | 8569-8681   |
|            |             |            |           |             | 8765-8875   |
|            |             |            |           |             | 8968-9037   |
|            |             |            |           |             | 9284-9499   |
|            |             |            |           |             | 9742-9910   |
|            |             |            |           |             | 10317-10501 |
|            |             |            |           |             | 10837-11187 |
|            |             |            |           |             | 11271-11321 |

|           |     |         |           |     | 11554-11707                |
|-----------|-----|---------|-----------|-----|----------------------------|
|           |     |         |           |     | 11783-12766                |
|           |     |         |           |     | 12866-13225                |
|           |     |         |           |     | 13256-13827                |
|           |     |         |           |     | 14284-14367                |
|           |     |         |           |     | 14890-15090                |
| HAUAI83   | 30  | 639009  | AC010422  | 783 | 1-315                      |
|           |     |         |           |     | 2004-2289                  |
|           |     |         |           |     | 2650-2741                  |
|           |     |         |           |     | 3554-3830                  |
| HAUAI83   | 30  | 639009  | AC010422  | 784 | 1-202                      |
|           |     |         |           |     | 938-1047                   |
|           |     |         |           |     | 1219-1395                  |
|           |     |         |           |     | 1758-1956                  |
|           |     |         |           |     | 2907-3429                  |
|           |     |         |           |     | 3792-3935                  |
|           |     |         |           |     | 5366-5485                  |
|           |     |         |           |     | 6391-6688                  |
|           |     |         |           |     | 6899-7269                  |
|           |     |         |           |     | 7890-8316                  |
|           |     |         |           |     | 8400-8524                  |
|           |     |         |           |     | 8607-8682                  |
|           |     |         |           |     | 8824-8999                  |
|           |     |         |           |     | 9190-9302                  |
|           |     |         |           |     | 9691-9796                  |
|           |     |         |           |     | 10106-10177                |
|           |     |         |           |     | 10571-11051                |
|           |     |         |           |     | 11164-11490                |
|           |     |         |           |     | 12565-12696                |
|           |     |         |           |     | 13364-13501                |
|           |     |         |           |     | 13964-14592                |
|           |     |         |           |     | 14740-15540                |
|           |     |         |           |     | 15610-15798                |
|           |     |         |           |     | 15947-16642                |
|           |     |         |           |     | 16717-16832<br>16968-17408 |
|           |     |         |           |     |                            |
|           |     |         |           |     | 17521-17612<br>18331-18579 |
|           |     |         |           |     | 19120-19303                |
|           |     |         |           |     | 19358-19514                |
|           |     |         |           |     | 19599-19702                |
|           |     |         |           |     | 20003-20245                |
| HAUAI83   | 30  | 639009  | AC018761  | 785 | 1-202                      |
| HAUA183   | 30  | 639009  | AC018/61  | /85 | 938-1047                   |
|           |     |         |           |     | 1219-1395                  |
|           |     |         |           |     | 1758-1956                  |
|           |     |         |           |     | 2907-3429                  |
|           |     |         |           |     | 3792-3935                  |
|           |     |         |           |     | 5366-5485                  |
|           |     |         |           | 1   | 6391-6688                  |
|           |     |         |           |     | 6899-7269                  |
|           |     |         |           |     | 7591-7711                  |
|           |     |         |           |     | 7890-8316                  |
|           |     |         |           | 1   | 8400-8524                  |
|           |     |         |           | 1   | 8607-8682                  |
|           |     |         |           |     | 8749-9073                  |
|           |     |         |           | 1   | 9190-9302                  |
|           |     |         |           | 1   | 9691-9796                  |
| HAUAI83   | 30  | 639009  | AC018761  | 786 | 1-82                       |
| 111011103 | 1 2 | 05,000, | 1.0010701 | 1   | 128-293                    |
|           |     |         |           |     | 1 120-233                  |

| HBINSS8 35 1352386 AL096774 787 1-1023 2010-2239 2-81-2962 3153-3234 3179-4726 HBINSS8 35 1352386 AL096774 788 1-341 HBINSS8 35 1352386 AL096774 789 1-142 11623G69 40 728432 AC068946 790 1-108 1186-1324 1746-1835 2138-2284 2448-2545 2718-2861 3091-5889 HC133G69 40 728432 AC068946 791 1-191 HC133G69 40 728432 AC068946 792 1-686 4643-4810 9339-9164 9382-9509 10587-1079 1153-11195 11265-11716 146441-15466 1745-1175-26 18012-1811 42053-02632 20957-21009 23696-23785 25398-25616 1745-1175-26 18012-1811 42053-02632 20957-2109 23696-23785 25398-25616 1745-1175-26 18012-1811 4644-15466 1745-1175-26 18012-1811 42053-02632 20957-2109 23696-23785 25398-25616 1745-1175-26 18012-1811 42053-02632 20957-2109 23696-23785 25398-26166 1745-1175-26 18012-1811 42053-02632 20957-2109 23696-23785 25398-26166 1745-1175-26 18012-1811 42053-02632 20957-2109 23696-23785 25398-26166 1745-1175-26 18012-1811 42053 2639-22644 43719-4571 4618-2568 6131-6578 8949-7003 9058-9726 14176-14460 1846-18915 1896-19871 22365-22454 23082-22248 28088-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368-28215 2368 |         |    |         |           |     |           |
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| HBINSS   35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |    |         |           |     |           |
| HBINSS8 35 1352386 AL096774 787 1-1023 2010-2239 2581-3962 3153-3223 3324-3493 3973-4126 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 41581-8582 |         |    |         |           |     |           |
| HDINSS8 35 1352386 AL096774 788 1-341 HBINSS8 35 1352386 AL096774 789 1-142 HCE3G69 40 728432 AC068946 790 1-108 HCE3G69 40 728432 AC068946 791 1-191 HCE3G69 40 728432 AC068946 791 1-191 HCE3G69 40 728432 AC068946 792 1-686 HCEF180 42 1143407 AL022327 793 1-2271 306-3658 4443-4810 9039-9164 9382-9509 10587-10720 1135-11195 11265-11716 1444-15466 17451-17526 18012-18114 20530-20632 20957-21009 23696-23785 25338-25573 25969-26166 7878-187 863-4508 1304-2003 280-3284 3719-4571 4618-2528 6131-6557 8947-903 9058-276 1476-14860 1846-18915 1860-19871 4618-2528 6131-6529 8949-7039 9058-726 1476-14860 1846-18915 1860-19871 22365-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22454 22082-22 |         |    |         |           |     |           |
| HBINSS8   35   1352386                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HBINS58 | 35 | 1352386 | AL096774  | 787 |           |
| HBINSS   35   1352386                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |    |         |           |     | 2010-2239 |
| HBINSS   35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |    |         |           |     | 2581-2962 |
| HBINSS   35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |    |         |           |     | 3153-3223 |
| HBINSS   35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |    |         |           |     | 3324-3493 |
| HBINSSS   35   1352386                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |    |         |           |     |           |
| HBINSS   35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | HBING58 | 35 | 1352386 | AT 006774 | 788 |           |
| HCB3G69 40 728432 AC068946 790 1-1686 1186-1324 1746-1835 2138-2284 2448-2545 2718-2861 3091-8889 HCB3G69 40 728432 AC068946 791 1-191                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |    |         |           |     |           |
| HCNDR47 47 1016919 AL122003 795 1.888 1.04.2003 9.058.716.72 1.91 1.92 1.93 1.93 1.93 1.93 1.93 1.93 1.93 1.93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |    |         |           |     |           |
| HCNDR47 47 1016919 AL122003 794 1-388 HCNDR47 47 1016919 AL122003 795 1-888 HCNDR47 48 1016919 AL122003 795 1-888 HCNDR47 49 1016919 AL122003 795 1-888 HCNDR47 47 1016919 AL122003 795 1-888                                                                                                                                                                                          | HCE3G69 | 40 | /20432  | AC066946  | /90 |           |
| HCE3G69 40 728432 AC068946 791 1-191 HCE3G69 40 728432 AC068946 792 1-686 HCEF1880 42 1143407 AL022327 793 1-2271 306-3658 444-34810 9039-9164 482-9509 10587-10720 2166-11736-11756-11756-1801-1814 20530-20632 20957-21009 2366-23785 2538-25575 2598-92-6166 7878-817 863-4508 5158-5744 6949-7029 HCNDR47 47 1016919 AL122003 794 1-236 531-696 7878-817 863-4508 5158-5744 6949-7039 9058-9726 14176-14480 1816-557 8947-9033 9058-9726 14176-14480 1816-557 8947-9033 9058-9726 14176-14480 1836-618915 18960-19871 22365-22454 22082-22348 22088-22454 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 22082-22484 2208 |         |    |         |           |     |           |
| HCNDR47 47 1016919 AL122003 795 1-888 1304-2003 181-858 46131-858 4718-2861 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261 4718-3261  |         |    |         |           |     |           |
| HCE3G69 40 728432 AC068946 791 1-191 HCE3G69 40 728432 AC068946 792 1-866 HCEFB80 42 1143407 AL022327 793 1-227 HCNDR47 47 1016919 AL122003 794 1-226 HCNDR47 47 1016919 AL122003 794 1-226 HCNDR47 47 1016919 AL122003 795 1-888 HCNDR47 47 1016919 AL122003 794 1-888 HCNDR47 47 1016919 AL122003 1-888 HCNDR47 47 1016919 A |         |    |         |           |     |           |
| HCE3G69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |    |         |           |     |           |
| HCB3G69 40 728432 AC068946 791 1-191 HCB3G69 40 728432 AC068946 792 1-686 HCEFB80 42 1143407 AL022327 793 3-1-227 HCEFB80 42 1143407 AL022327 793 3-1-237 350-6368 4643-8190 10587-10720 10587-10720 1155-11756 1265-11716 146444-15466 17451-17526 18012-18114 20530-20632 20957-21009 23696-23785 2538-25575 2598-926166 7878-817 863-4508 515-88-744 6949-7029 HCNDR47 47 1016919 AL122003 795 1-888 1304-2003 2830-3284 3719-4571 4618-5268 6131-6557 8947-9033 9058-9726 14176-14480 18456-18915 1860-19871 22365-22454 22088-22154 1800-22-2248 22088-22154 22082-22248 22088-22154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22082-22248 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-222154 22088-2 |         |    |         |           |     |           |
| HCB3G69 40 728432 AC068946 792 1-686 HCEFB80 42 1143407 AL022327 793 1-2271 3506-3668 4643-4810 9039-9164 9882-9509 10587-10720 11135-11195 11265-11716 14644-15466 17451-17526 18012-18114 20530-20632 20957-21009 23696-23785 25338-25575 25969-26166 7878-817 863-3508 5158-5744 6949-7029 47 1016919 AL122003 794 1-236 531-696 7878-817 863-3508 1304-2003 2830-3284 3719-4571 4618-3268 6131-6557 8947-9033 9058-9726 1476-14450 18466-18915 1860-19871 22365-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 22088-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 2208-22454 220 |         |    |         |           |     |           |
| HCNDR47 47 1016919 AL122003 795 1-888 1094-909-2046 14176-14919 AL122003 795 1-888 1094-909-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2049-919-2 |         |    |         |           |     |           |
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| HCNDR47 47 1016919 AL122003 794 1-236 5138-24509 HCNDR47 47 1016919 AL122003 794 1-236 5138-2573 471-471-471-471-471-471-471-471-471-471-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |    |         |           |     | 3506-3658 |
| HCNDR47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |    |         |           |     | 4643-4810 |
| HCNDR47 47 1016919 AL122003 794 1236.450.8518.518.518.518.518.518.518.518.518.51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |    |         |           |     | 9039-9164 |
| HCNDR47 47 1016919 AL122003 794 1236.450.8518.518.518.518.518.518.518.518.518.51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |    |         |           |     | 9382-9509 |
| HCNDR47 47 1016919 AL122003 794 1-236 HCNDR47 47 1016919 AL122003 794 1-236 HCNDR47 47 1016919 AL122003 795 1-888 1518-57-44 6949-7029 HCNDR47 47 1016919 AL122003 795 1-888 1516-57-45 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-56 1516-5 |         |    |         |           |     |           |
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| HCNDR47 47 1016919 AL122003 794 1-236 HCNDR47 47 1016919 AL122003 794 1-236 HCNDR47 47 1016919 AL122003 795 1-888 1518-58-744 6949-7029 478-178-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88-88-159-88 |         |    |         |           |     |           |
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| HCNDR47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |    |         |           |     |           |
| HCNDR47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |    |         |           |     |           |
| Company                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |    |         |           |     |           |
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| HCNDR47 47 1016919 AL122003 795 1-88<br>104-2003 2830-3284<br>3719-4571<br>4618-3268<br>6131-6557<br>8947-9033<br>9058-9726<br>14176-14480<br>18456-18915<br>18960-19871<br>22365-22454<br>23082-23248<br>28088-28215<br>HDPGT01 61 771583 AC020978 796 1-1800                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |    |         |           |     |           |
| HCNDR47 47 1016919 AL122003 795 1-888 1304-2003 2830-3284 3719-4571 4618-3268 6131-6557 8947-9033 9058-9726 14176-14480 18456-18915 18960-19871 22365-22454 23082-23248 28088-28215 HDPGT01 61 771583 AC020978 796 1-1800                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |    |         |           |     |           |
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| HDPGT01 61 771583 AC020978 796 1-880                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |    |         |           |     | 6949-7029 |
| HDPGT01 61 771583 AC020978 796 1-880                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HCNDR47 | 47 | 1016919 | AL122003  | 795 |           |
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| HDPGT01 61 771583 AC020978 796 1-180 4618-5278 44618-5278 6131-6557 8947-9033 9058-9726 14176-14480 18456-18915 18960-19871 23365-22454 23082-23248 28058-28215 1-180 2776-2899                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |    |         |           |     |           |
| 6131-6557<br>8947-9033<br>9058-9726<br>14176-14480<br>18456-18915<br>18960-19871<br>22365-22454<br>23082-23248<br>24088-28215<br>HDPGT01 61 771583 AC020978 796 1-180<br>2776-2899                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |    |         |           |     |           |
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| HDPGT01 61 771583 AC020978 796 1.180                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |    |         |           |     |           |
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| 22365-22454<br>  23082-23248<br>  28088-28215<br>  HDPGT01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1       |    |         |           | 1   |           |
| 23082-23248<br>  28088-28215<br>  HDPGT01   61   771583   AC020978   796   1-180<br>  2776-2899                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |    |         |           |     |           |
| 28058-28215<br>  HDPGT01   61   771583   AC020978   796   1-180<br>  2776-2899                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |    |         |           |     |           |
| HDPGT01 61 771583 AC020978 796 1-180 2776-2899                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |    |         |           |     |           |
| 2776-2899                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |    |         |           |     |           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPGT01 | 61 | 771583  | AC020978  | 796 |           |
| 3016.4077                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |    |         |           |     |           |
| 3910-40//                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |    |         |           | İ   | 3916-4077 |

|                    |          |                   |                      |            | 4296-4335              |
|--------------------|----------|-------------------|----------------------|------------|------------------------|
|                    |          |                   |                      |            | 4436-4632              |
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| HDPGT01            | 61       | 771583            | AC020978             | 797        | 1-384                  |
| HDPSB18            | 67       | 1043263           | AL355512             | 798        | 1-2572                 |
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| HDPSB18            | 67       | 1043263           | AC006176             | 799        | 1-2571                 |
|                    | l        |                   |                      |            | 3048-3872              |
| HDPSB18            | 67       | 1043263           | AL355512             | 800        | 1-280                  |
| HDPXY01            | 74       | 879048            | AL354000             | 801        | 1-1319                 |
|                    |          |                   |                      |            | 4848-4975              |
|                    |          |                   |                      |            | 5229-5600              |
|                    |          |                   |                      |            | 6561-6654              |
| HDPXY01            | 74       | 879048            | AL035362             | 802        | 1-1316                 |
|                    |          |                   |                      |            | 4844-4971              |
|                    |          |                   |                      |            | 5225-5596              |
| ****               |          | 0=00.00           |                      |            | 6557-6650              |
| HDPXY01            | 74       | 879048            | AL354000             | 803        | 1-460                  |
| HDPXY01            | 74       | 879048            | AL354000             | 804        | 1-400                  |
| HDPXY01            | 74       | 879048            | AL035362             | 805        | 1-400                  |
| HDPXY01            | 74<br>93 | 879048<br>1011487 | AL035362             | 806<br>807 | 1-460                  |
| HFIIN69            | 93       | 1011487           | AC027797             | 808        | 1-1438<br>1-329        |
| HFIIN69<br>HHBCS39 | 104      | 1003028           | AC027797<br>AL390960 | 809        | 1-329                  |
| HHBCS39            | 104      | 1003028           | AL358992             | 810        | 1-2979                 |
| HHBCS39            | 104      | 1003028           | AL358992             | 811        | 1-2983                 |
| HHGCG53            | 110      | 340818            | AC024037             | 812        | 1-518                  |
| HHGCM76            | 111      | 662329            | AC003665             | 813        | 1-70                   |
| IIIIGCW176         | 1111     | 002329            | ACOUSOUS             | 613        | 304-609                |
|                    |          |                   |                      |            | 900-1090               |
|                    |          |                   |                      |            | 1240-1835              |
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| HHGCM76            | 111      | 662329            | AC003665             | 814        | 1-580                  |
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|                    |          |                   |                      |            | 1314-1663              |
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|                    |          |                   |                      |            | 5121-5230<br>5331-5689 |
| HJACG30            | 116      | 895505            | AC018512             | 815        | 1-776                  |
| HJACG30            | 116      | 895505<br>895505  | AC022305             | 816        | 1-776                  |
| HJACG30            | 116      | 895505            | AC022303<br>AC002518 | 817        | 1-8/8                  |
| HLTIP94            | 137      | 1087335           | AC007431             | 818        | 1-130                  |
| HLTIP94            | 137      | 1087335           | AC007431             | 819        | 1-1299                 |
| HMSDL37            | 154      | 973996            | AC012086             | 820        | 1-3328                 |
| HMSDL37            | 154      | 973996            | AC012086<br>AC018811 | 821        | 1-3328                 |
| HMSDL37            | 154      | 973996            | AC018494             | 822        | 1-3029                 |
| THEODES!           | 1.77     | 713770            | /10010474            | 022        | 1-3029                 |

|              | 54 973996<br>54 973996<br>54 973996 | AC012086<br>AC012086<br>AC018811 | 823<br>824 | 1-224<br>1-468         |
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| HMSDL37 1:   |                                     |                                  |            |                        |
|              | 54   973996                         |                                  |            |                        |
| HMSDL37   14 |                                     |                                  | 825        | 1-222                  |
|              |                                     | AC018811                         | 826        | 1-468                  |
|              | 54 973996                           | AC018494                         | 827        | 1-224                  |
|              | 54 973996                           | AC018494                         | 828        | 1-1854                 |
|              | 72 1041375                          | AC003675                         | 829        | 1-2128                 |
|              | 72 1041375                          | AC001228                         | 830        | 1-2129                 |
| HNGOI12 1    |                                     | AC013791                         | 831        | 1-2132                 |
|              | 74 664507                           | AC020552                         | 832        | 1-290                  |
|              | 74 664507                           | AC020552                         | 833        | 1-96                   |
| HNTSY18 13   | 33 1041383                          | AC004877                         | 834        | 1-175                  |
|              |                                     |                                  |            | 342-474                |
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|              |                                     |                                  |            | 5032-5164              |
|              |                                     |                                  |            | 6664-6820              |
|              |                                     |                                  |            | 7288-7881              |
| HNTSY18 13   | 3 1041383                           | AC004877                         | 835        | 1-42                   |
| 11113116     | 1041363                             | AC004677                         | 655        | 1197-1333              |
|              |                                     |                                  |            | 1575-1698              |
|              |                                     |                                  |            | 1936-1984              |
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| HOHBY44 18   | 89 873264                           | AC074201                         | 836        | 1-5280                 |
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| HOHBY44 18   | 89 873264                           | AC074201                         | 837        | 1-298                  |
| HPJBK12 19   | 07 1011467                          | AC022033                         | 838        | 1-2649                 |
| HPJBK12 19   | 07 1011467                          | AC013541                         | 839        | 1-2649                 |
| HPJBK12 19   |                                     | AC022033                         | 840        | 1-190                  |
|              | 07 1011467                          | AC013541                         | 841        | 1-190                  |
| HPJCL22      | 08 1146674                          | AC037447                         | 842        | 1-102                  |
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|              |                                     |                                  |            | 995-1315               |
|              |                                     |                                  |            | 1450-1567              |
| 1            |                                     |                                  |            | 2189-2515              |
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|              |                                     |                                  |            | 10277-10988            |
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|              |                                     |                                  |            | 12592-13077            |
| HPJCL22 19   | 98 1146674                          | AC022400                         | 843        | 1-102                  |
|              | 1                                   | 1                                | I          | 373-826                |
|              | 1                                   |                                  | l          |                        |
|              |                                     |                                  |            | 995-1315<br>1450-1567  |

|         |       |         |          |      | 2189-2515   |
|---------|-------|---------|----------|------|-------------|
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|         |       |         |          |      | 11874-12473 |
|         |       |         |          |      | 12591-13076 |
| HPJCL22 | 198   | 1146674 | AC037447 | 844  | 1-207       |
| HPJCL22 | 198   | 1146674 | AC037447 | 845  | 1-2124      |
| HPJCL22 | 198   | 1146674 | AC022400 | 846  | 1-207       |
| HPJCL22 | 198   | 1146674 | AC022400 | 847  | 1-2124      |
|         |       |         |          | · ·  | 2470-2567   |
|         |       |         |          |      | 2865-2971   |
| HPRAL78 | 200   | 1352342 | AC007783 | 848  | 1-2334      |
|         |       |         |          |      | 2508-3084   |
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|         |       |         |          |      | 7298-7392   |
|         |       |         |          |      | 7730-7846   |
|         |       |         |          |      | 9147-9476   |
|         |       |         |          |      | 10487-10575 |
|         |       |         |          |      | 10791-11298 |
|         |       |         |          |      | 11485-11601 |
|         |       |         |          |      | 11783-13009 |
|         |       |         |          |      | 13207-13501 |
|         |       |         |          |      | 13540-13772 |
|         |       |         |          |      | 14439-14800 |
|         |       |         |          |      | 14923-14983 |
|         |       |         |          |      | 15133-15355 |
|         |       |         |          |      | 15485-15653 |
|         |       |         |          |      | 16750-16805 |
|         |       |         |          |      | 16894-17078 |
|         |       |         |          |      | 17162-17219 |
|         |       |         |          |      | 18003-18089 |
|         |       |         |          |      | 21085-21146 |
|         |       |         |          |      | 21358-21501 |
| HPRAL78 | 200   | 1352342 | AC007783 | 849  | 1-308       |
| HPRAL78 | 200   | 1352342 | AC007783 | 850  | 1-1024      |
| HRGBL78 | 204   | 910133  | AL359541 | 851  | 1-1024      |
| HKGDL/8 | 204   | 910133  | AL339341 | 0.51 | 2777-3307   |
|         |       |         |          |      | 3670-3823   |
|         |       |         |          |      | 4113-4385   |
|         |       |         |          |      | 4844-5381   |
|         |       |         |          |      | 5995-7365   |
| HSAWD74 | 207   | 460527  | AC004951 | 852  |             |
| nsawd/4 | 1 207 | 400327  | AC004931 | 832  | 1-1651      |

|         |     |        |          |     | 1740-2593   |
|---------|-----|--------|----------|-----|-------------|
| HSAWD74 | 207 | 460527 | AC004951 | 853 | 1-149       |
| HSAWD74 | 207 | 460527 | AC004951 | 854 | 1-5057      |
|         |     |        |          |     | 5082-8353   |
|         |     |        |          |     | 8404-8996   |
| HTPCS72 | 240 | 854941 | AL008639 | 855 | 1-106       |
|         |     |        |          |     | 1457-1595   |
|         |     |        |          |     | 1666-2484   |
|         |     |        |          |     | 2910-3006   |
|         |     |        |          |     | 3705-4147   |
|         |     |        |          |     | 4768-5141   |
|         |     |        |          |     | 5304-5536   |
|         |     |        |          |     | 5746-5874   |
|         |     |        |          |     | 7114-7241   |
|         |     |        |          |     | 7468-7711   |
|         |     |        |          |     | 7963-8746   |
|         |     |        |          |     | 9438-12408  |
|         |     |        |          |     | 12884-14976 |
| HTPCS72 | 240 | 854941 | AL008639 | 856 | 1-720       |
| HTPIH83 | 241 | 919916 | AL158821 | 857 | 1-1862      |
|         |     |        |          |     | 1880-3126   |

[0089] Table 1D: The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists ould be used to treat the associated disease.

[0090] The present invention encompasses methods of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating diabetes mellitus comprising administering to a patient in which such detection, treatment, prevention, and/or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate diabetes mellitus.

[0091] In another embodiment, the present invention also encompasses methods of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; comprising administering to a patient <u>combinations</u> of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in Column 3 of Table ID.

[1092] Table ID provides information related to biological activities for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table ID also provides information related to assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("CDNA Clone ID.") provides the unique clone identifier for each clone as previously described and indicated in Table IA through Table ID. The third column ("AA SEQ ID NO.Y.") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding

cDNA clones (also as indicated in Tables 1A, Table 1B, and Table 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity.

[0093] Table 1D describes the use of, inter alia, FMAT technology for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT) is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound flurophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. See, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using flourometric microvolume assay technology." Journal of Biomolecular Screening; 4:193-204 (1999). In particular, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)). [00941 Table 1D also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK. ERK, and p38 Kinase Activities" Biol. Chem. 379(8-9): 1101-1110 (1998).

| Gene No. | cDNA Clone ID | AA SEQ ID | Biological Activity    | Exemplary Activity Assay                | Preferred Indication                   |
|----------|---------------|-----------|------------------------|-----------------------------------------|----------------------------------------|
|          | H2CB1183      | NO: Y     | Stimulation of insulin | Assavs for measuring secretion of       | A highly preferred indication is       |
|          |               |           | secretion from         | insulin are well-known in the art and   | diabetes mellitus. An                  |
|          |               |           | pancreatic beta cells. | may be used or routinely modified to    | additional highly preferred indication |
|          |               |           |                        | assess the ability of polypeptides of   | is a complication associated with      |
|          |               |           |                        | the invention (including antibodies     | diabetes (e.g., diabetic retinopathy,  |
|          |               |           |                        | and agonists or antagonists of the      | diabetic nephropathy, kidney disease   |
|          |               |           |                        | invention) to stimulate insulin         | (e.g., renal failure, nephropathy      |
|          |               |           |                        | secretion. For example, insulin         | and/or other diseases and disorders as |
|          |               |           |                        | secretion is measured by FMAT           | described in the "Renal Disorders"     |
|          |               |           |                        | using anti-rat insulin antibodies.      | section below), diabetic neuropathy,   |
|          |               |           |                        | Insulin secretion from pancreatic beta  | nerve disease and nerve damage         |
|          |               |           |                        | cells is upregulated by glucose and     | (e.g., due to diabetic neuropathy),    |
|          |               |           |                        | also by certain proteins/peptides, and  | blood vessel blockage, heart disease,  |
|          |               |           |                        | disregulation is a key component in     | stroke, impotence (e.g., due to        |
|          |               |           |                        | diabetes. Exemplary assays that may     | diabetic neuropathy or blood vessel    |
|          |               |           |                        | be used or routinely modified to test   | blockage), seizures, mental            |
|          |               |           |                        | for stimulation of insulin secretion    | confusion, drowsiness, nonketotic      |
|          |               |           |                        | (from pancreatic cells) by              | hyperglycemic-hyperosmolar coma,       |
|          |               |           |                        | polypeptides of the invention           | cardiovascular disease (e.g., heart    |
|          |               |           |                        | (including antibodies and agonists or   | disease, atherosclerosis,              |
|          |               |           |                        | antagonists of the invention) include   | microvascular disease, hypertension,   |
|          |               |           |                        | assays disclosed in: Ahren, B., et al., | stroke, and other diseases and         |
|          |               |           |                        | Am J Physiol, 277(4 Pt 2):R959-66       | disorders as described in the          |
|          |               |           |                        | (1999); Li, M., et al., Endocrinology,  | "Cardiovascular Disorders" section     |
|          |               |           |                        | 138(9):3735-40 (1997); Kim, K.H.,       | below), dyslipidemia, endocrine        |
|          |               |           |                        | et al., FEBS Lett, 377(2):237-9         | disorders (as described in the         |
|          |               |           |                        | (1995); and, Miraglia S et. al.,        | "Endocrine Disorders" section          |
|          |               |           |                        | Journal of Biomolecular Screening,      | below), neuropathy, vision             |
|          |               |           |                        | 4:193-204 (1999), the contents of       | impairment (e.g., diabetic retinopathy |
|          |               |           |                        | each of which is herein incorporated    | and blindness), ulcers and impaired    |
|          |               |           |                        | by reference in its entirety.           | wound healing, and infection (e.g.,    |
|          |               |           |                        | Pancreatic cells that may be used       | infectious diseases and disorders as   |
|          |               |           |                        | according to these assays are publicly  | described in the "Infectious           |
|          |               |           |                        |                                         |                                        |

| 406 Regulation of viability and poliferation of purcreate befared is. | malder may be routinely gueened. Ecomplary pancreatic cells that may cheened are according to the season, and a contraction. Ecomplary pancreatic cells that may cheened are INS-1 cells. INS-1 cells. INS-1 cells in a contraction. An additional institution of the real mediation is obseived in the cash distribution cells for a mediate in the cells from institution. These cells centime the cells from institution. These cells centime the cells from the cell | Assays for the regulation of vibality and and proliferation of cells in vitro and proliferation of cells in vitro and and proliferation of cells in vitro and and proliferation of cells in vitro and the complete of the comp |
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|                                                                       | avalable (e.g., through the ATCC<br>and/or may be routinely generated<br>Exemplary puncreatic cells that m<br>be used accounting to these assays<br>include rat INS-1 cells. INS-1 cells. INS-1 cells<br>are a sem-abherent cell info<br>esublished from cells isolated from<br>a X-ray induced rat transplantal<br>insultanca. These cells retain<br>charesteries typical of mative<br>puncreatic beat cells including<br>glucose inducible insultangent<br>References. Ashari et al.<br>Frederences. Ashari et al.<br>Indoorundogy 1992 1301 et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 406                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|   |         |     |                        | et al Mol Endocrinol 15(1):136-48       | "Cardiovascular Disorders" section     |
|---|---------|-----|------------------------|-----------------------------------------|----------------------------------------|
|   |         |     |                        | (2001); Huotari MA, et al.,             | below), dyslipidemia, endocrine        |
|   |         |     |                        | Endocrinology, 139(4):1494-9            | disorders (as described in the         |
|   |         |     |                        | (1998); Hugl SR, et al., J Biol Chem    | "Endocrine Disorders" section          |
|   |         |     |                        | 1998 Jul 10;273(28):17771-9 (1998),     | below), neuropathy, vision             |
|   |         |     |                        | the contents of each of which is        | impairment (e.g., diabetic retinopathy |
|   |         |     |                        | herein incorporated by reference in     | and blindness), ulcers and impaired    |
|   |         |     |                        | its entirety. Pancreatic cells that may | wound healing, and infection (e.g.,    |
|   |         |     |                        | be used according to these assays are   | infectious diseases and disorders as   |
|   |         |     |                        | publicly available (e.g., through the   | described in the "Infectious           |
|   |         |     |                        | ATCCTM) and/or may be routinely         | Diseases" section below, especially    |
|   |         |     |                        | generated. Exemplary pancreatic         | of the urinary tract and skin), carpal |
|   |         |     |                        | cells that may be used according to     | tunnel syndrome and Dupuytren's        |
|   |         |     |                        | these assays include rat INS-1 cells.   | contracture). An additional highly     |
|   |         |     |                        | INS-1 cells are a semi-adherent cell    | preferred indication is obesity and/or |
|   |         |     |                        | line established from cells isolated    | complications associated with          |
|   |         |     |                        | from an X-ray induced rat               | obesity. Additional highly preferred   |
|   |         |     |                        | transplantable insulinoma. These        | indications include weight loss or     |
|   |         |     |                        | cells retain characteristics typical of | alternatively, weight gain. Additional |
|   |         |     |                        | native pancreatic beta cells including  | highly preferred indications are       |
|   |         |     |                        | glucose inducible insulin secretion.    | complications associated with insulin  |
|   |         |     |                        | References: Asfari et al.               | resistance.                            |
|   |         |     |                        | Endocrinology 1992 130:167.             |                                        |
|   | H6EDC19 | 406 | Proliferation of pre-  | Assays for the regulation (i.e.         |                                        |
| 2 |         |     | adipose cells (such as | increases or decreases) of viability    |                                        |
|   |         |     | 3T3-L1 cells)          | and proliferation of cells in vitro are |                                        |
|   |         |     |                        | well-known in the art and may be        |                                        |
|   |         |     |                        | used or routinely modified to assess    |                                        |
|   |         |     |                        | the ability of polypeptides of the      |                                        |
|   |         |     |                        | invention (including antibodies and     |                                        |
|   |         |     |                        | agonists or antagonists of the          |                                        |
|   |         |     |                        | invention) to regulate viability and    |                                        |
|   |         |     |                        | proliferation of pre-adipose cells and  |                                        |
|   |         |     |                        | cell lines. For example, the            |                                        |
|   |         |     |                        | CellTiter-Gloô Luminescent Cell         |                                        |
|   |         |     |                        | Viability Assay (Promega Corp.,         |                                        |
|   |         |     |                        | Madison, WI, USA) can be used to        |                                        |

| Activation of transcription through cAMP response element in immune |
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| celle (euch as Tacelle)                                             |

| inclubing authodics and agonism or an automotion properation or automotion of automotion.  Exemplary assays for transcription automotion.  Exemplary assays for transcription of guess involved in a welf-wursty of coAMP response element that may be used or routinely medical to see the invention (including ambieved and agonism or automotion of the casters are publicly available (e.g., through are perfectly of the automotion of the casters are publicly available (e.g., through are perfectly of the automotion of the casters are publicly available (e.g., through are perfectly of the automotion of the casters are publicly available (e.g., through are perfectly of the automotion of the casters are publicly available (e.g., through are perfectly of the automotion of the casters are publicly available (e.g., through are perfectly of the automotion of the casterion of the cas |
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|   |         |     |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | arthrifts, AIDs, granulomatous arthrifts, AIDs, granulomatous arthrifts, AIDs, granulomatous beat disease, inflummonto bebed disease, sepsis, incutrophilia, sergiss, neutrophilia, sergiss, neutrophilia, neutrophi |
|---|---------|-----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| m | HACBD91 | 407 | Production of IL-6 | cells and has stonge effects on Be<br>cells and has stonge effects on B<br>cells. L. G. portification in LL-<br>induced lgf. production (gd. phys a robe in<br>muccod lgf. production (gd. phys a robe in<br>muccosal immunity). IL-6 induces<br>expression of LL-6 has been linked to<br>copyression of LL-6 has been linked to<br>morniumme disease, plearue-0500mas,<br>myolomas, and denon dealers. Asseys<br>for municondulatory and<br>differentiation factor products<br>differentiation factor products<br>where the expression level is stongly? | he highly proferred unbediment of the invention includes a method for the invention includes a method for method for including (e.g., increasing) ILL-6 production. An alternative bighty production. An alternative bighty producted enhodiment of the invention includes a method for invention includes a method for production. A highly proferred including (e.g., producing) ILL-6 production. A highly proferred indications include enhancement of museral immunity. Highly preferred indications include below mader furname Activity. Perform and disorders (e.g. as described below mader Turnum Activity.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|   |         |     |                    | Regulated by Goldanes, growin<br>fluctors, and hormones are well<br>fluctors, and hormones are well<br>forward in the season of the con-<br>rollinely of polypeadus of the<br>invention (including autholicies and<br>invention) (including autholicies of<br>invention) to mediate<br>invention) to mediate<br>differentiation and modulate Tell<br>differentiation and modulate Tell<br>differentiation and modulate Tell<br>function. Its season is that test for<br>Exemplary assays that test for                                                    | underon (e.g., as escribed now<br>wettered nickalonios hindre<br>perfect dicidations hindre<br>perfect dicidations hindre<br>automimum dicisase (e.g.,<br>automimum dicisase) (e.g.,<br>automimum dicisase) (e.g.,<br>immum deficiencies (e.g.,<br>immum deficiencies (e.g.,<br>indrativos) and<br>indications also include boosting a B<br>indications also include boosting a B<br>alternatively suppressing a B cell-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| mediated immune response. Highly perfered infeatuous include inflammation and inflammation and inflammation inflammation and inflammation inflammation indicates Additional lighly preferred indications include sathma and indications include sathma and indications include resplicate (i.g., proposition factories (e.g., proposition factories) include any proposition of the perferred indications include a propriate and cancers, such as a myoloma, had proposition and concercis such in myoloma, palamonia, and prostate, heaves, lung, colon, pancrettic, beass, lung, colon, pan | disections include beingin debe beingin des des gebendes des des des des des des des des des                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and regregation or 1 Cell prodiferation and inactional activities. Such as and inactional activities. Such assays that may be used or routinely modified to test immunomodulatory modified to test immunomodulatory polypsyches of the invention include assays disclosed in invention include assays disclosed in thire and agoniss or ammonates of the invention include assays disclosed in Miraglia et al., 204(1999), Rowland et al., 204(1999), Rowland et al., 204(1999), Rowland et al., 204(1999), Rowland et al., Chaphrocycers a practical approach (Chapter 6), 38-160 (2000), and Chapter 6), Il minumod 1582-9192-925 (1997), the contents                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | to clean of which are been in morporated by reference in its interview. Human dead in clean is a clearly Human dead according to these may be used according to these may be used according to these stays may be is abanded using techniques (sieslosed herein or morporate provincia) and the art. Human deadwise clean as a suggest prosesting or as a suggest provincial in a suggest provincial and a pregulational and activities. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

|   |         |     |                                                                 |                                                                                                       | indication is infection (e.g., an<br>infectious disease as described below<br>under "Infectious Disease"). |
|---|---------|-----|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| 3 | HACBD91 | 407 | Regulation of<br>transcription of Malic<br>Enzyme in adinocytes | Assays for the regulation of<br>transcription of Malic Enzyme are<br>well-known in the art and may be | A highly preferred indication is<br>diabetes mellitus. An<br>additional highly preferred indication        |
|   |         |     | ·                                                               | used or routinely modified to assess<br>the ability of polypeptides of the                            | is a complication associated with<br>diabetes (e.g., diabetic retinopathy,                                 |
|   |         |     |                                                                 | agonists or antagonists of the invention) to regulate transcription of                                | (e.g., renal failure, nephropathy                                                                          |
|   |         |     |                                                                 | Manie Enzyme, a key enzyme m<br>lipogenesis. Malic enzyme is<br>involved in lipogenesisand its        | section below), diabetic neuropathy,<br>nerve disease and nerve damage                                     |
|   |         |     |                                                                 | expression is stimulted by insulin.  ME promoter contains two direct                                  | (e.g., due to diabetic neuropathy),<br>blood vessel blockage, heart disease,                               |
|   |         |     |                                                                 | repeat (DR1)- like elements MEp<br>and MEd identified as putative PPAR                                | stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel                                     |
|   |         |     |                                                                 | response elements. ME promoter<br>may also responds to AP1 and other                                  | blockage), seizures, mental<br>confusion, drowsiness, nonketotic                                           |
|   |         |     |                                                                 | transcription factors. Exemplary assays that may be used or routinely                                 | hyperglycemic-hyperosmolar coma,<br>cardiovascular disease (e.g., heart                                    |
|   |         |     |                                                                 | modified to test for regulation of<br>transcription of Malic Enzyme (in                               | disease, atherosclerosis,<br>microvascular disease, hypertension,                                          |
|   |         |     |                                                                 | adipoocytes) by polypeptides of the<br>invention (including antibodies and                            | stroke, and other diseases and<br>disorders as described in the                                            |
|   |         |     |                                                                 | agonists or antagonists of the                                                                        | "Cardiovascular Disorders" section                                                                         |
|   |         |     |                                                                 | in: Streeper, R.S., et al., Mol                                                                       | disorders (as described in the                                                                             |
|   |         |     |                                                                 | Garcia-Jimenez, C., et al., Mol                                                                       | below), neuropathy, vision                                                                                 |
|   |         |     |                                                                 | Endocrinol, 8(10):1361-9 (1994);<br>Barroso, I., et al., J Biol Chem,                                 | impairment (e.g., diabetic retinopathy<br>and blindness), ulcers and impaired                              |
|   |         |     |                                                                 | 274(25):17997-8004 (1999);                                                                            | wound healing, and infection (e.g.,                                                                        |
|   |         |     |                                                                 | (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)                                                               | infectious diseases and disorders as<br>described in the "Infectious                                       |
|   |         |     |                                                                 | Berger, et al., Gene 66:1-10 (1988);                                                                  | Diseases" section below, especially                                                                        |

|   |         |     |                                                                     | and Clints, It, et al. Methods in<br>Enzymol. 216:362–368 (1992), the<br>countries of each of which is herein<br>incorporated by reference in its<br>enterity. Hepatocytes that may be<br>used according to these assays are<br>used according to these assays are<br>used according to these assays are<br>actively with the countries of the<br>ATCCV9 and/or may be routinely<br>generated. Exemplary hepatocytes<br>in may be used according to these<br>assays includes the 14HE rat liver<br>is a proposed to the contract of the<br>entering the countries of the countries of the<br>supervised. Exemplary hepatocytes<br>assays includes the 14HE rat liver                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | tumed syntheore and Duppytren's conventional and the conventional to the convention associated with obesity. Additional highly preferred indications included weight loss or alternatively, weight gain.  Additional highly preferred additional highly preferred additional highly preferred and additional highly preferred additional highly preferred with a south the convention of |
|---|---------|-----|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| m | HACBO91 | 407 | Activation of England States of England States of Englands Fathway. | Kinese assay. JNK and p38 kinase assay. JNK and p38 kinase regulate cell proliferation, activation regulate cell proliferation, activation and apoptosis are well known in the art and apoptosis are well known in the art may be used or routinely prolife to assass the ability of polypeptides of the invention of the control of the properties and agonists or antagonists of the invention) to provide a proposition of the properties and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Esemphary activation, and apoptosis. Esemphary many provides of the invention of proliferation activity of polyperpides of manyle to test MN and p38 kinase induced activity of polyperpides of the rememor of prolifering amplocities and agonists or antagonists of the activation in the Rener et al. Biol Chem and the properties of the | A highly preferred embodiment of stimmlating encloseds a method for the weeting in budges a method for the weeting in budges a method for the medium of the invention includes a method for invention includes a method for invention includes in method for invention includes in method for invention includes a method for infinity geopotosis of endothelial cells. An intigation proposition of the invention includes a method for infinity included in method for including edge.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| -                                                                     | n preferred embodiment of the<br>invention includes a method for            | inhibiting (e.g., decreasing) the | activation of and/or inactivating    | preferred embodiment o             | invention includes a method for   | stimulating angiogenisis. An     |                          | Ť                                   | includes a metho                   | angiogenesis. A highly preferred    | embodiment of the invention        | includes a method for reducing   | cardiac hypertrophy. An alternative | highly preferred embodiment of the | invention includes a method for | inducing cardiac hypertrophy. | Highly preferred indications include | neoplastic diseases (e.g., as described | below under "Hyperproliferative | Disorders"), and disorders of the | cardiovascular system (e.g., heart | disease, congestive heart failure, | hypertension, aortic stenosis, | cardiomyopathy, valvular | regurgitation, left ventricular | dysfunction, atherosclerosis and | atherosclerotic vascular disease, | diabetic nephropathy, intracardiac | shunt, cardiac hypertrophy, | myocardial infarction, chronic | hemodynamic overload, and/or as | described below under | "Cardiovascular Disorders"). Highly |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|--------------------------------------|------------------------------------|-----------------------------------|----------------------------------|--------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|----------------------------------|-------------------------------------|------------------------------------|---------------------------------|-------------------------------|--------------------------------------|-----------------------------------------|---------------------------------|-----------------------------------|------------------------------------|------------------------------------|--------------------------------|--------------------------|---------------------------------|----------------------------------|-----------------------------------|------------------------------------|-----------------------------|--------------------------------|---------------------------------|-----------------------|-------------------------------------|
| Mol Biol 71(3-4):479-500 (1999),<br>the contents of each of which are | herein incorporated by reference in<br>its entirety. Endothelial cells that | may be used according to these    | assays are publicly available (e.g., | endothelial cells that may be used | according to these assays include | human umbilical vein endothelial | cells (HUVEC), which are | endothelial cells which line venous | blood vessels, and are involved in | functions that include, but are not | limited to, angiogenesis, vascular | permeability, vascular tone, and | immune cell extravasation.          |                                    |                                 |                               |                                      |                                         |                                 |                                   |                                    |                                    |                                |                          |                                 |                                  |                                   |                                    |                             |                                |                                 |                       |                                     |
|                                                                       |                                                                             |                                   |                                      |                                    |                                   |                                  |                          |                                     |                                    |                                     |                                    |                                  |                                     |                                    |                                 |                               |                                      |                                         |                                 |                                   |                                    |                                    |                                |                          |                                 |                                  |                                   |                                    |                             |                                |                                 |                       | _                                   |
|                                                                       |                                                                             |                                   |                                      |                                    |                                   |                                  |                          |                                     |                                    |                                     |                                    |                                  |                                     |                                    |                                 |                               |                                      |                                         |                                 |                                   |                                    |                                    |                                |                          |                                 |                                  |                                   |                                    |                             |                                |                                 |                       |                                     |

| - |  | preferred indications include           |
|---|--|-----------------------------------------|
|   |  | conditional on definition and ton       |
|   |  | cardiovascular, endomenal and/or        |
|   |  | angiogenic disorders (e.g., systemic    |
|   |  | disorders that affect vessels such as   |
|   |  | diabetes mellitus, as well as diseases  |
|   |  | of the vessels themselves, such as of   |
|   |  | the arteries, capillaries, veins and/or |
|   |  | lymphatics). Highly preferred are       |
|   |  | indications that stimulate              |
|   |  | angiogenesis and/or                     |
|   |  | cardiovascularization. Highly           |
|   |  | preferred are indications that inhibit  |
|   |  | angiogenesis and/or                     |
|   |  | cardiovascularization. Highly           |
|   |  | preferred indications include           |
|   |  | antiangiogenic activity to treat solid  |
|   |  | tumors, leukemias, and Kaposi"s         |
|   |  | sarcoma, and retinal disorders.         |
|   |  | Highly preferred indications include    |
|   |  | neoplasms and cancer, such as,          |
|   |  | Kaposi"s sarcoma, hemangioma            |
|   |  | (capillary and cavernous), glomus       |
|   |  | tumors, telangiectasia, bacillary       |
|   |  | angiomatosis,                           |
|   |  | hemangioendothelioma,                   |
|   |  | angiosarcoma,                           |
|   |  | haemangiopericytoma,                    |
|   |  | lymphangioma, lymphangiosarcoma.        |
|   |  | Highly preferred indications also       |
|   |  | include cancers such as, prostate,      |
|   |  | breast, lung, colon, pancreatic,        |
|   |  | esophageal, stomach, brain, liver,      |
|   |  | and urinary cancer. Preferred           |
|   |  | indications include benign              |
|   |  | dysproliferative disorders and pre-     |
|   |  | neoplastic conditions, such as, for     |
|   |  | example, hyperplasia, metaplasia,       |

| indications include blood disorders  (e.g. as described bloow under  "Immune Adrity", "Blood-Related  "Booders", and "Cardiovascular  Disorders", and "Cardiovascular  Disorders", "Brettered indications  Inductor and adritis, systemic lupus  and an adritis, systemic lupus  and or as described below) and  farmandeficiencis (e.g., as  described below). Additional  preferred indications include  inflammation and inflammator  disorders (e.g., as and end chronic  inflammation and inflammator  disorders (e.g., as and end chronic  inflammatory basess, e.g.,  inflammatory bowel disease and  chronic stages and  disorders (e.g., as and end printing  disorders) (e.g., as and end end end  disorders) (e.g., as and end end  disorders) (e.g., as and end end  disorders) (e.g., as and  disorders) (e.g., as an | A highly preferred emboliment<br>of the invention includes a method of<br>the invention includes a method of<br>strainmaint of cell proliferation.<br>An alternative highly preferred<br>and alternative highly preferred and alternative of the<br>methods a method for inhibiting T and alternative of the<br>includes a method for inhibiting T preferred emboliment of the<br>invention includes a method for a<br>mention includes a method for a<br>method includes a method for a<br>method includes a method for<br>inhibiting the activation of and/or<br>inhibiting the activation of the<br>strainhaling (e.g., increasing) III.2<br>strainhaling (e.g., increasing) III.2<br>preferred embodiment of the |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transacription through the CD28 transacription through the CD28 transacription through the CD28 the state of the transacription through the CD28 the state of the transacription through the properties of the invention polypequides of the invention producing analysis of the invention of summlate IL-2 expression in Teells among the CD38 response element through the CD38 response element through the CD38 response element increment including the properties of the invention (including ambodies of the invention (including ambodies of the invention) include assays disclosed in invention include assays disclosed in what making the cell (1998).                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transarijani unidi<br>transarijani unidi<br>102 sepanse element<br>in immune celis (sach<br>as T-eclis).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 407                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HACBD91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | m                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| Hernbrom et al., Proc bald Acade Sign (1987) and 216-23-68 (1982). Hernbrom et al., Proc bald Acade Sign (1987) and Leodelli. I Immunol 106-245 (1982). McGuire and Leodelli. I Immunol 106-2377-2343 (2001), and Diacker et al., J Biolin Chama (1982) and Diacker et al., J Biolin Chama | d Sci inhibiting (e.g., reducing) IL-2 cGuire production Additional highly                  | preferred indica         |                               | 3iol indications include autoimmune diseases (e.g., rheumatoid arthritis. | rein                          | _                               |                                 | _                               |                              | these immine response. An additional | _                           | of infection (e.g., AIDS, and/or as | _                              | Disease"). Highly preferred | indications include neoplastic | diseases (e.g., melanoma, renal cell | carcinoma, leukemia, lymphoma, | and/or as described below under | "Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as, for | example, melanoma (e.g., metastatic | melanoma), renal cell carcinoma | (e.g., metastatic renal cell | carcinoma), leukemia, lymphoma | (e.g., T cell lymphoma), and prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver and | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | nevalactic conditions such as for |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------|-------------------------------|---------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|------------------------------|--------------------------------------|-----------------------------|-------------------------------------|--------------------------------|-----------------------------|--------------------------------|--------------------------------------|--------------------------------|---------------------------------|----------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|---------------------------------|------------------------------|--------------------------------|----------------------------------------|----------------------------------|---------------------------------------|---------------------------------|----------------------------|-------------------------------------|-----------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Enzymol 216;362-368 (1992)<br>Henthom et al., Proc Natl Aca<br>USA 85-6342-6346 (1988). Aca | and Jacobelli, J Immunol | al., J Immunol 166(4):2437-22 | (2001); and Butscher et al., J I<br>Chem 3(1):552-560 (1998), th          | contents of each of which are | incorporated by reference in it | entirety. T cells that may be u | according to these assays are I | available (e.g., through the | that may be used according to        | assays include the JURKAT o | which is a suspension culture       | leukemia cells that produce IL | when stimulated.            |                                |                                      |                                |                                 |                                  |                                      |                                     |                                     |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     |                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                             |                          |                               |                                                                           |                               |                                 |                                 |                                 |                              |                                      |                             |                                     |                                |                             |                                |                                      |                                |                                 |                                  |                                      |                                     |                                     |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     | _                                 |

|   |         |     |                        |                                      | example, hyperplasia, metaplasia,        |
|---|---------|-----|------------------------|--------------------------------------|------------------------------------------|
|   |         |     |                        |                                      | and/or dysplasia. A highly               |
|   |         |     |                        |                                      | preferred indication is infection (e.g., |
|   |         |     |                        |                                      | tuberculosis, infections associated      |
|   |         |     |                        |                                      | with granulomatous disease, and          |
|   |         |     |                        |                                      | osteoporosis, and/or an infectious       |
|   |         |     |                        |                                      | disease as described below under         |
|   |         |     |                        |                                      | "Infectious Disease"). A highly          |
|   |         |     |                        |                                      | preferred indication is AIDS.            |
|   |         |     |                        |                                      | Additional highly preferred              |
|   |         |     |                        |                                      | indications include suppression of       |
|   |         |     |                        |                                      | immune reactions to transplanted         |
|   |         |     |                        |                                      | organs and/or tissues, uveitis,          |
|   |         |     |                        |                                      | psoriasis, and tropical spastic          |
|   |         |     |                        |                                      | paraparesis. Preferred indications       |
|   |         |     |                        |                                      | include blood disorders (e.g., as        |
|   |         |     |                        |                                      | described below under "Immune            |
|   |         |     |                        |                                      | Activity", "Blood-Related                |
|   |         |     |                        |                                      | Disorders", and/or "Cardiovascular       |
|   |         |     |                        |                                      | Disorders"). Preferred indications       |
|   |         |     |                        |                                      | also include anemia, pancytopenia,       |
|   |         |     |                        |                                      | leukopenia, thrombocytopenia,            |
|   |         |     |                        |                                      | Hodgkin's disease, acute                 |
|   |         |     |                        |                                      | lymphocytic anemia (ALL),                |
|   |         |     |                        |                                      | plasmacytomas, multiple myeloma,         |
|   |         |     |                        |                                      | Burkitt's lymphoma, arthritis,           |
|   |         |     |                        |                                      | granulomatous disease, inflammatory      |
|   |         |     |                        |                                      | bowel disease, sepsis, neutropenia,      |
|   |         |     |                        |                                      | neutrophilia, hemophilia,                |
|   |         |     |                        |                                      | hypercoagulation, diabetes mellitus,     |
|   |         |     |                        |                                      | endocarditis, meningitis, Lyme           |
|   |         |     |                        |                                      | Disease, asthma and allergy.             |
|   | HACBD91 | 407 | Activation of          | Assays for the activation of         | Highly preferred indications             |
| 3 |         |     | transcription through  | transcription through the Nuclear    | include blood disorders (e.g., as        |
|   |         |     | NFAT response          | Factor of Activated T cells (NFAT)   | described below under "Immune            |
|   |         |     | element in immune      | response element are well-known in   | Activity", "Blood-Related                |
|   |         |     | cells (such as natural | the art and may be used or routinely | Disorders", and/or "Cardiovascular       |
|   |         |     |                        |                                      |                                          |

| Disorders"). Highly preferred disclassive indiacions included autoimmule discases (e.g. rheumatoid arthritis discases (e.g. rheumatoid arthritis servenic lupus experime in properties discarbide below), immunodeficiencies (e.g., as described below), immunodeficiencies (e.g., as described below), prosenting a Toell-mediated immune response, and arthritis discussing at Cell-mediated immune response, and immune response, and immune response, and discincial infanty preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | disorders. An additional highly, disorders. An additional highly experted influention is infection (e.g., an infection disease as described below under "Historians Disease"). Preferred influents include responsing disease (e.g., londering hymbioma, and/or is described hymbioma, and/or is described. Disorders', Preferred indications                                            | include neoplasms and cancers, such ask, eve cample, leukemin, lymphorna, and prostate herests, lungs, coop, parevated, esophageal, stoop, parevated, esophageal, esophageal, esophageal, esophageal, esophageal, esophageal, perferred indications also include aremin, puncytoparia, and checkperia, humonocytoparia, thoughen, leukedperia, humonocytoparia, flodgán is disease, acute. Hodgán is disease, acute. Parevated in the propocula manie (ALL). Plasmacytomia, milipér myelona.                          |
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| modified to assess the ability of polypeptides of the invention (including antibodies and agonists or authorities and agonists or authorities and agonists or expandence of the control of | polypepixies of the invention<br>clinitian and an area of the control and an analysis of the invention) include<br>analysis of the invention) include<br>Gene 66:1-10 (1998); Culten and<br>Manth, Methods in Engynet of all,<br>216:362-368 (1992); Henthem et al.,<br>216:362-368 (1992); Henthem et al.,<br>Pre-Nul A, Anal S, et al. N. 85:542-<br>6346 (1988); Annibut et al., Ess. | Med 18(2)/801/810 (1995), D. Med 18(2)/801/810 (1995), The Poet et al., Int J Biochem Cell Biol 31(10)):221-1236 (1996), Fraser et (1999), and Yesern et al., J Biol Demon 20/9/288-844 (1999), and Yesern et al., J Biol Demon 20/9/288-14293 (1993), the contents of each of which are been incorporated by reference in its entirety. MK cells that may be therein incorporated by reference in its entirety. MK cells that may be about a content of these assays are publicly available (e.g., frought the ATCCT <sup>3</sup> ). Exemplary human NK cells from the exet according to these assays include the NK-7T cell child may with closely according to the exet according to the exet according to the exet according to the which is a human manual killer cell line with cytolytic and cytotoxic |
| killer cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|   |         |     |                           | activity.                              | Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, Dsoriasis, suppression |
|---|---------|-----|---------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
|   |         |     |                           |                                        | of immune reactions to transplanted<br>organs and tissues, hemophilia,                                                                            |
|   |         |     |                           |                                        | hypercoagulation, diabetes mellitus,<br>endocarditis meningitis I vane                                                                            |
|   |         |     |                           |                                        | Disease, asthma and allergy.                                                                                                                      |
|   | HACBD91 | 407 | Activation of             | Assays for the activation of           | A preferred embodiment of the                                                                                                                     |
| 3 |         |     | transcription through     | transcription through the Serum        | invention includes a method for                                                                                                                   |
|   |         |     | serum response element    | Response Element (SRE) are well-       | inhibiting (e.g., reducing) TNF alpha                                                                                                             |
|   |         |     | in immune cells (such     | known in the art and may be used or    | production. An alternative highly                                                                                                                 |
|   |         |     | as natural killer cells). | rounnely moduled to assess the         | presented embodiment of the                                                                                                                       |
|   |         |     |                           | invention (including antibodies and    | stimulating (e.g. increasing) TNF                                                                                                                 |
|   |         |     |                           | agonists or antagonists of the         | alpha production. Preferred                                                                                                                       |
|   |         |     |                           | invention) to regulate serum           | indications include blood disorders                                                                                                               |
|   |         |     |                           | response factors and modulate the      | (e.g., as described below under                                                                                                                   |
|   |         |     |                           | expression of genes involved in        | "Immune Activity", "Blood-Related                                                                                                                 |
|   |         |     |                           | growth and upregulate the function     | Disorders", and/or "Cardiovascular                                                                                                                |
|   |         |     |                           | of growth-related genes in many cell   | Disorders"), Highly preferred                                                                                                                     |
|   |         |     |                           | types. Exemplary assays for            | indications include autoimmune                                                                                                                    |
|   |         |     |                           | transcription through the SRE that     | diseases (e.g., rheumatoid arthritis,                                                                                                             |
|   |         |     |                           | may be used or routinely modified to   | systemic lupus erythematosis,                                                                                                                     |
|   |         |     |                           | test SRE activity of the polypeptides  | Crohn"s disease, multiple sclerosis                                                                                                               |
|   |         |     |                           | of the invention (including antibodies | and/or as described below),                                                                                                                       |
|   |         |     |                           | and agonists or antagonists of the     | immunodeficiencies (e.g., as                                                                                                                      |
|   |         |     |                           | invention) include assays disclosed in | described below), boosting a T cell-                                                                                                              |
|   |         |     |                           | Berger et al., Gene 66:1-10 (1998);    | mediated immune response, and                                                                                                                     |
|   |         |     |                           | Cullen and Malm, Methods in            | suppressing a T cell-mediated                                                                                                                     |
|   |         |     |                           | Enzymol 216:362-368 (1992);            | immune response. Additional highly                                                                                                                |
|   |         |     |                           | Henthorn et al., Proc Natl Acad Sci    | preferred indications include                                                                                                                     |
|   |         |     |                           | USA 85:6342-6346 (1988); Benson        | inflammation and inflammatory                                                                                                                     |
|   |         |     |                           | et al., J Immunol 153(9):3862-3873     | disorders, and treating joint damage                                                                                                              |
|   |         |     |                           | (1994); and Black et al., Virus Genes  | in patients with rheumatoid arthritis.                                                                                                            |
|   |         |     |                           | 12(2):105-117 (1997), the content of   | An additional highly preferred                                                                                                                    |

| indication is sepsis. Highly | preferred indications include    | neoplastic diseases (e.g., leukemia, | lymphoma, and/or as described          | below under "Hyperproliferative | Disorders"). Additionally, highly | preferred indications include  | neoplasms and cancers, such as, for | example, leukemia, lymphoma,         | melanoma, glioma (e.g., malignant | glioma), solid tumors, and prostate, | breast, hmg, colon, pancreatic, | esophageal, stomach, brain, liver and | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia, | pancytopenia, leukopenia, | thrombocytopenia, Hodgkin's | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple | myeloma, Burkitt's lymphoma, | arthritis, AIDS, granulomatous | disease, inflammatory bowel disease, | neutropenia, neutrophilia, psoriasis, | suppression of immune reactions to | transplanted organs and tissues, | hemophilia, hypercoagulation, | diabetes mellitus, endocarditis, | meningitis, Lyme Disease, cardiac | reperfusion injury, and asthma and | allergy. An additional preferred | indication is infection (e.g., an | infectious disease as described below |
|------------------------------|----------------------------------|--------------------------------------|----------------------------------------|---------------------------------|-----------------------------------|--------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|--------------------------------------|---------------------------------|---------------------------------------|---------------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------------|--------------------------------|------------------------------|--------------------------------|--------------------------------------|---------------------------------------|------------------------------------|----------------------------------|-------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|-----------------------------------|---------------------------------------|
| each of which are herein     | incorporated by reference in its | entirety. T cells that may be used   | according to these assays are publicly | available (e.g., through the    | ATCCTM). Exemplary T cells that   | may be used according to these | assays include the NK-YT cell line, | which is a human natural killer cell | line with cytolytic and cytotoxic | activity.                            |                                 |                                       |                                 |                            |                                     |                                     |                                   |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       |                                    |                                  |                               |                                  |                                   |                                    |                                  |                                   |                                       |
|                              |                                  |                                      |                                        |                                 |                                   |                                |                                     |                                      |                                   |                                      |                                 |                                       |                                 |                            |                                     |                                     |                                   |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       |                                    |                                  |                               |                                  |                                   |                                    |                                  |                                   |                                       |
|                              |                                  |                                      |                                        |                                 |                                   |                                |                                     |                                      |                                   |                                      |                                 |                                       |                                 |                            |                                     |                                     |                                   |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       |                                    |                                  |                               |                                  |                                   |                                    |                                  |                                   | _                                     |
|                              |                                  |                                      |                                        |                                 |                                   |                                |                                     |                                      |                                   |                                      |                                 |                                       |                                 |                            |                                     |                                     |                                   |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       |                                    |                                  |                               |                                  |                                   |                                    |                                  |                                   | _                                     |

| under "Infectious Disease"). | Preterred indications include<br>neonlastic diseases (e.g., as described | below under "Hyperproliferative    | Disorders"), blood disorders (e.g., as | described below under "Immune     | Activity", "Cardiovascular    | Disorders", and/or "Blood-Related     | Disorders"), and infection (e.g., an | infectious disease as described below | under "Infectious Disease"). Highly | preferred indications include | autoimmune diseases (e.g.,           | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below) and | immunodeficiencies (e.g., as          | described below). Additional highly   | preferred indications include      | inflammation and inflammatory   | disorders. Highly preferred | indications also include neoplastic  | discases (e.g., leukemia, lymphoma, | and/or as described below under      | "Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as,    | leukemia, lymphoma, prostate,       | breast, lung, colon, pancreatic,      | esophageal, stomach, brain, liver,   | and urinary cancer. Other preferred | indications include benign     | dysproliferative disorders and pre-  | neoplastic conditions, such as, for         | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred           | indications include arthritis, asthma, |
|------------------------------|--------------------------------------------------------------------------|------------------------------------|----------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|-------------------------------------|-------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|-----------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|--------------------------------------|---------------------------------------------|-----------------------------------|---------------------------------------|----------------------------------------|
|                              | Assays for the activation of<br>transcription through the AP1            | response element are well-known in | the art and may be used or routinely   | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to     | modulate growth and other cell        | functions. Exemplary assays for     | transcription through the AP1 | response element that may be used or | routinely modified to test AP1-      | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1988); Cullen and | Malm, Methods in Enzymol    | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Rellahan et al., J Biol | Chem 272(49):30806-30811 (1997); | Chang et al., Mol Cell Biol          | 18(9):4986-4993 (1998); and Fraser | et al., Eur J Immunol 29(3):838-844 | (1999), the contents of each of which | are herein incorporated by reference | in its entirety. Human T cells that | may be used according to these | assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ). Exemplary | human T cells that may be used    | according to these assays include the | SUPT cell line, which is an IL-2 and   |
|                              | Activation of<br>transcription through                                   | AP1 response element               | in immune cells (such                  | as T-cells).                      |                               |                                       |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                             |                                   |                                       |                                        |
|                              | 407                                                                      |                                    |                                        |                                   |                               |                                       |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                             |                                   |                                       |                                        |
| 100000                       | HACBD91                                                                  |                                    |                                        |                                   |                               |                                       |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                             |                                   |                                       |                                        |
|                              | en                                                                       |                                    |                                        |                                   |                               |                                       |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                             |                                   |                                       |                                        |

| sperssion-culture. A LDNS allengy, meaning, another properties, leukopening, thomboeytopenin, leukopening, leukopening, leukopening, leukopening, leukopening, leukopening, leukopening, garandomatons, septis, postraise, sappression of immune reactions to trensplanted meaning and treated in the sections of the sections | A highly perferred etmodiment of the invention includes a method from the ability of the invention includes a method from the invention includes a method for including the area of the invention includes a method for including the area of the invention includes a method for including the area of the invention includes a method for including the area of the invention includes a method for including the area of the invention includes a method of including the artivation of and/or including the artivation of the preferred embediane of the preferred embediane of the production. Additional highly preferred information and inflummation and inflummation and inflummation and inflummation and including anchined and artiful preferred inflummation and including anchined and artiful preferred and artiful preferred including anchined artiful and artiful preferred including anchined artiful and ar |
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| II.4 responsive suspension-culture cell line.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Advision of Assays for the activation of Individual and against so the activation of Individual authorities and againsts or including authorities and againsts or including authorities and against so including authorities and against so including authorities and against so including authorities of the invention) to simulate LL2 copression in Cells.  International activation of the Assays for transcription intrough the CD28 response element and may be used ro routinely modified to test CD28-response element and against so of the prevention (including ambodies of the invention (including ambodies and Agains to and Agains to act againsts of the invention include assays disclosed in Engineer et al., Celle et activation of the Against and Adam Against and Against and Adam Against and Adam Against and Against and Adam Against and Adam Against and Adam Against and Adam Against and Against and Adam Against and Against a |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HACBD91 407 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | o.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| Committee Control in nounger in n | Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used                | diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as a described below), immunodeficiencies (e.g., as a described below), immunodeficiencies (e.g., as a described below), becoming Toul |
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| accond<br>available<br>ATCC<br>that ma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | according to these assays are properly available (e.g., through the ATCC <sup>TM</sup> ). Exemplary human T cells that may be used according to these | mediated immune response, and suppressing a T cell-mediated immune response, and immune response. Highly                                                                                                                                                                            |
| assays<br>which is<br>and IL.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | assays include the SOPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.                                                 | preterred indications include neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                       | betow time of "typeynolicrative Disorders"). Highly preferred indications include nooplasms and cancers, such as, for example, medanoma e.g., meastatic melanoma, renal cell carcinoma                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                       | (e.g., metastatic renal cell<br>carcinoma, lettechnia, lymphona<br>(e.g., T cell lymphona), and prostac,<br>bress, lung, colon, pnarceatic,<br>esophageal, stomach, brain, liver and<br>unirary cancer. Other preferred<br>indications include benigm                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                       | dysproliterative disorders and pre-<br>neoplastic conditions, such as, for<br>example, hyperplasta, metaplasta,<br>and/or dysplasta. A highly<br>preferred indication includes<br>infection (e.g., AIDS, tuberculosis,<br>infection associated with                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                       | granulomatous disease, and osteoporosis, and/or as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred                                                                                                                  |

|   |         |     |                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | immure rescions to transplanted organs and or transplanted organs and or itsuses truching organs and or itsuses truching organs and or itsuses truching purposess, and trupical grastic purposess. Preferred indications include blood discusses (Preferred indications or desertied below under 'Immune Arstriy' 'Basod-Selekated Discusters', Preferred indications also include arcmit, pancytoperati, pancytoperatik,  |
|---|---------|-----|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| m | HACBD91 | 407 | Activation of remarking the Manachino though NFAT response element in immune cells (such as F-cells). | Assays for the activation of remarkable to Nuclear Pactor of Activated T cells (NFAT) response element are well-known in the art and may be used or noutinely modified to assess the ability of pupplyndise of the invention (including anthodies and agoniss or distributions and agoniss or capalate NFAT remacription factors and modulate expression of genes and modulate expression of genes in modulate expression of genes in modulate expression of genes in modulate actors and modulate actors in the activation of the public fluid on the activation of the public fluid on the activation of the public fluid on the public fluid on the public fluid on the public fluid on the public fluid | Highly preferred indications Highly preferred indications Highly preferred indications described blood disorders (e.g., as described blood disorders (e.g., as described blood winder "Immune Activity", "Blood-Related Disorders, and our Cantilovascular Disorders, and our Cantilovascular Disorders, "Highly preferred diseases (e.g., rheumanoid arthritis, andrigh esclerosis and or as described below), immunodeficiencies (e.g., na mediated immune response, and mediated immune response, and minimum response, and immune response, and im |

| Highly preferred indications                                     | Assays for the activation of                                  | Activation of | 40/  | HACBD91 |  |
|------------------------------------------------------------------|---------------------------------------------------------------|---------------|------|---------|--|
| Disease, asthma and allergy.                                     |                                                               | :             | 1000 | 100000  |  |
| and coordition manipolitic Lymn                                  |                                                               |               | _    |         |  |
| organs and tissues, hemophilia,                                  |                                                               |               |      |         |  |
| of immune reactions to transplanted                              |                                                               |               |      |         |  |
| neutrophilia, psoriasis, suppression                             |                                                               |               |      |         |  |
| bowel disease, sepsis, neutropenia,                              |                                                               |               |      |         |  |
| granulomatous disease, inflammatory                              |                                                               |               |      |         |  |
| Burkitt's lymphoma, arthritis, AIDS,                             | cells.                                                        |               |      |         |  |
| plasmacytomas, multiple myeloma,                                 | culture of IL-2 and IL-4 responsive T                         |               |      |         |  |
| lymphocytic anemia (ALL),                                        | SUPT cell line, which is a suspension                         |               |      |         |  |
| Hodgkin's disease, acute                                         | according to these assays include the                         |               |      |         |  |
| also include anemia, pancytopenia,<br>lenkonenia rhmmhocytonenia | unough the AICC.**). Exemplary human T cells that may be used |               |      |         |  |
| dysplasia. Preferred indications                                 | assays are publicly available (e.g.,                          |               |      |         |  |
| hyperplasia, metaplasia, and/or                                  | may be used according to these                                |               |      |         |  |
| conditions, such as, for example,                                | reference in its entirety. T cells that                       |               |      |         |  |
| disorders and pre-neoplastic                                     | which are herein incorporated by                              |               |      |         |  |
| include benign dysproliferative                                  | 14293 (1993), the contents of each of                         |               |      |         |  |
| cancer. Other preferred indications                              | al., J Biol Chem 268(19):14285-                               |               |      |         |  |
| stomach, brain, liver and urinary                                | 29(3):838-844 (1999); and Yeseen et                           |               |      |         |  |
| colon, pancreatic, esophageal,                                   | Fraser et al., Eur J Immunol                                  |               |      |         |  |
| lymphoma, and prostate, breast, lung,                            | Biol 31(10):1221-1236 (1999);                                 |               |      |         |  |
| as, for example, leukemia,                                       | De Boer et al., Int J Biochem Cell                            |               |      |         |  |
| include neoplasms and cancers, such                              | Biophys Acta 1498(1):1-18 (2000);                             |               |      |         |  |
| Disorders"), Preferred indications                               | 6346 (1988): Serfling et al., Biochim                         |               |      |         |  |
| below under "Hyperproliferative                                  | Proc Natl Acad Sci USA 85:6342-                               |               |      |         |  |
| neoplastic diseases (e.g., leukemia,                             | Malm, Methods in Enzymol                                      |               |      |         |  |
| Preferred indications include                                    | Gene 66:1-10 (1998); Cullen and                               |               |      |         |  |
| below under "Infectious Disease").                               | assays disclosed in Berger et al.,                            |               |      |         |  |
| an infectious disease as described                               | antagonists of the invention) include                         |               |      |         |  |
| preferred indication is infection (e.g.,                         | (including antibodies and agonists or                         |               |      |         |  |
| disorders. An additional highly                                  | polypeptides of the invention                                 |               |      |         |  |
| inflammation and inflammatory                                    | response element activity of                                  |               |      |         |  |
| preferred indications include                                    | routinely modified to test NFAT-                              |               |      |         |  |
|                                                                  |                                                               |               |      |         |  |

| include inflammation and | inflammatory disorders. Highly        | preferred indications include blood | disorders (e.g., as described below | ınder "Immune Activity", "Blood- | Related Disorders", and/or                | 'Cardiovascular Disorders"). Highly | preferred indications include         | autoimmune diseases (e.g.,   | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis    | and/or as described below), and     | immunodeficiencies (e.g., as      | described below). An additional  | highly preferred indication is        | infection (e.g., AIDS, and/or an       | infectious disease as described below | under "Infectious Disease"). | Highly preferred indications include | neoplastic diseases (e.g., melanoma, | eukemia, lymphoma, and/or as | described below under                 | "Hyperproliferative Disorders").      | Highly preferred indications include | neoplasms and cancers, such | as,melanoma, renal cell carcinoma, | eukemia, lymphoma, and prostate, | breast, lung, colon, pancreatic,            | esophageal, stomach, brain, liver and | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for     | example, hyperplasia, metaplasia,          | and/or dysplasia. Preferred                | indications also include anemia, | zancyropema, reuvopema, |
|--------------------------|---------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------------------|-------------------------------------|---------------------------------------|------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|----------------------------------|---------------------------------------|----------------------------------------|---------------------------------------|------------------------------|--------------------------------------|--------------------------------------|------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|-----------------------------|------------------------------------|----------------------------------|---------------------------------------------|---------------------------------------|---------------------------------|----------------------------|-------------------------------------|-----------------------------------------|--------------------------------------------|--------------------------------------------|----------------------------------|-------------------------|
| $\vdash$                 | response element are well-known in in |                                     | Jo                                  | -                                | (including antibodies and agonists or   R | antagonists of the invention) to    | regulate NFKB transcription factors p | and modulate expression of a | immunomodulatory genes.              | Exemplary assays for transcription e | through the NFKB response element a | that may be used or rountinely ir | modified to test NFKB-response d | element activity of polypeptides of h | the invention (including antibodies ir | and agonists or antagonists of the    | d in                         | 368);                                |                                      |                              | Henthorn et al., Proc Natl Acad Sci d | USA 85:6342-6346 (1988); Black et   " |                                      | _                           | je<br>Je                           | =                                | reference in its entirety. T cells that   b | Ť                                     |                                 | Ž.                         | human T cells that may be used d    | according to these assays include the n | SUPT cell line, which is a suspension   c. | culture of IL-2 and IL-4 responsive T   a: | cells.                           | 41                      |
| transcription through    | NFKB response                         | element in immune                   | cells (such as T-cells).            |                                  |                                           |                                     |                                       |                              |                                      |                                      |                                     |                                   |                                  |                                       |                                        |                                       |                              |                                      |                                      |                              |                                       |                                       |                                      |                             |                                    |                                  |                                             |                                       |                                 |                            |                                     |                                         |                                            |                                            |                                  |                         |
|                          |                                       |                                     |                                     |                                  |                                           |                                     |                                       |                              |                                      |                                      |                                     |                                   |                                  |                                       |                                        |                                       |                              |                                      |                                      |                              |                                       |                                       |                                      |                             |                                    |                                  |                                             |                                       |                                 |                            |                                     |                                         |                                            |                                            |                                  |                         |
| -                        |                                       |                                     |                                     |                                  |                                           |                                     |                                       |                              |                                      |                                      |                                     |                                   |                                  |                                       |                                        |                                       |                              |                                      |                                      |                              |                                       |                                       |                                      |                             |                                    |                                  |                                             |                                       |                                 |                            |                                     |                                         |                                            |                                            |                                  |                         |
| 3                        |                                       |                                     |                                     |                                  |                                           |                                     |                                       |                              |                                      |                                      |                                     |                                   |                                  |                                       |                                        |                                       |                              |                                      |                                      |                              |                                       |                                       |                                      |                             |                                    |                                  |                                             |                                       |                                 |                            |                                     |                                         |                                            |                                            |                                  |                         |

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|---|---------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------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| m | HACBD91 | 407 | Activation of Target in the Carlo State of State | Assessy for the activation of Transduces and Activation of Transduces and Activations of Transduces and Activations of Transduces and Activations of Chinacipion (STATO) is exponse element are well-known in the art and may be used or rouninely modified to assess the ability of poppedace of the invention (including ambodies and agoniss or authories and agoniss or authories and agoniss or authories and agoniss or regulate STAT6 transcription floors and agoniss or multiple genes. Exemplazy assays for transcription through the STAT6 reposes element man be used or countriely modified to test STAT6 or tousinely modified to test STAT6 poppedices of the invention of the polypoptides of the invention including amploods and agonists or autagoniss of the invention including amploods and agonists or authoring modes and agonists or authoring and Machole State and Activity of the polypoptides of the invention include and authority and Report et al. | A highly preferred indication is allergy.  Another highly preferred indication is assiming the definition of the definit                                             |

|   |         |     |                   | Proc Natl Acad Sci USA 85:6342-         | neoplasms and cancers, such as,          |
|---|---------|-----|-------------------|-----------------------------------------|------------------------------------------|
|   |         |     |                   | 6346 (1988); Georas et al., Blood       | leukemia, lymphoma, melanoma, and        |
|   |         |     |                   | 92(12):4529-4538 (1998); Moffatt et     | prostate, breast, lung, colon,           |
|   |         |     |                   | al., Transplantation 69(7):1521-1523    | pancreatic, esophageal, stomach,         |
|   |         |     |                   | (2000); Curiel et al., Eur J Immunol    | brain, liver and urinary cancer. Other   |
|   |         |     |                   | 27(8):1982-1987 (1997); and Masuda      | preferred indications include benign     |
|   |         |     |                   | et al., J Biol Chem 275(38):29331-      | dysproliferative disorders and pre-      |
|   |         |     |                   | 29337 (2000), the contents of each of   | neoplastic conditions, such as, for      |
|   |         |     |                   | which are herein incorporated by        | example, hyperplasia, metaplasia,        |
|   |         |     |                   | reference in its entirety. T cells that | and/or dysplasia.                        |
|   |         |     |                   | may be used according to these          | Preferred indications include anemia,    |
|   |         |     |                   | assays are publicly available (e.g.,    | pancytopenia, leukopenia,                |
|   |         |     |                   | through the ATCCTM). Exemplary T        | thrombocytopenia, Hodgkin's              |
|   |         |     |                   | cells that may be used according to     | disease, acute lymphocytic anemia        |
|   |         |     |                   | these assays include the SUPT cell      | (ALL), plasmacytomas, multiple           |
|   |         |     |                   | line, which is a suspension culture of  | myeloma, Burkitt's lymphoma,             |
|   |         |     |                   | IL-2 and IL-4 responsive T cells.       | arthritis, AIDS, granulomatous           |
|   |         |     |                   |                                         | disease, inflammatory bowel disease,     |
|   |         |     |                   |                                         | sepsis, neutropenia, neutrophilia,       |
|   |         |     |                   |                                         | psoriasis, suppression of immune         |
|   |         |     |                   |                                         | reactions to transplanted organs and     |
|   |         |     |                   |                                         | tissues, hemophilia,                     |
|   |         |     |                   |                                         | hypercoagulation, diabetes mellitus,     |
|   |         |     |                   |                                         | endocarditis, meningitis, and Lyme       |
|   |         |     |                   |                                         | Disease. An additional                   |
|   |         |     |                   |                                         | preferred indication is infection (e.g., |
|   |         |     |                   |                                         | an infectious disease as described       |
|   |         |     |                   |                                         | below under "Infectious Disease").       |
|   | HACCI17 | 408 | Activation of     | Kinase assay. Kinase assays, for        | A highly preferred embodiment            |
| 4 |         |     | Adipocyte ERK     | example an Elk-1 kinase assay, for      | of the invention includes a method       |
|   |         |     | Signaling Pathway | ERK signal transduction that regulate   | for stimulating adipocyte                |
|   |         |     |                   | cell proliferation or differentiation   | proliferation. An alternative highly     |
|   |         |     |                   | are well known in the art and may be    | preferred embodiment of the              |
|   |         |     |                   | used or routinely modified to assess    | invention includes a method for          |
|   |         |     |                   | the ability of polypeptides of the      | inhibiting adipocyte proliferation.      |
|   |         |     |                   | invention (including antibodies and     | A highly preferred embodiment of         |
|   |         |     |                   | agonists or antagonists of the          | the invention includes a method for      |

| stimulating adipocyte differentiation. An alternative highly preferred  | embodiment of the invention           | includes a method for inhibiting     | adipocyte differentiation. A      | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below<br>under "Infectious Disease"). |
|-------------------------------------------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|---------------------------------------------------------------------|
| invention) to promote or inhibit cell<br>proliferation, activation, and | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                                                            |
|                                                                         |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                                                     |
|                                                                         |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                                                     |

| ind | diabetes mentions. An additional | inginy preferred indication is a | diahetes (e.g., diahetic retinopathy | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication |
|-----|----------------------------------|----------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|---------------------------------------|------------------------------------|----------------------------------------|
|     |                                  |                                  |                                      |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |
|     |                                  |                                  |                                      |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |
|     |                                  |                                  |                                      |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |

|   |         |     |                       |                                        | associated with obesity. Additional highly preferred indications include |
|---|---------|-----|-----------------------|----------------------------------------|--------------------------------------------------------------------------|
|   |         |     |                       |                                        | weight loss or alternatively, weight                                     |
|   |         |     |                       |                                        | gain. Additional highly                                                  |
|   |         |     |                       |                                        | preserved indications are<br>complications associated with insulin       |
|   |         |     |                       |                                        | resistance. Additional highly                                            |
|   |         |     |                       |                                        | preferred indications are disorders of                                   |
|   |         |     |                       |                                        | the musculoskeletal systems                                              |
|   |         |     |                       |                                        | including myopathies, muscular                                           |
|   |         |     |                       |                                        | dystrophy, and/or as described                                           |
|   |         |     |                       |                                        | herein. Additional highly                                                |
|   |         |     |                       |                                        | preferred indications include,                                           |
|   |         |     |                       |                                        | hypertension, coronary artery                                            |
|   |         |     |                       |                                        | disease, dyslipidemia, gallstones,                                       |
|   |         |     |                       |                                        | ostcoarthritis, degenerative arthritis,                                  |
|   |         |     |                       |                                        | cating disorders, fibrosis, cachexia,                                    |
|   |         |     |                       |                                        | and kidney diseases or disorders.                                        |
|   |         |     |                       |                                        | Preferred indications include                                            |
|   |         |     |                       |                                        | neoplasms and cancer, such as,                                           |
|   |         |     |                       |                                        | lymphoma, leukemia and breast,                                           |
|   |         |     |                       |                                        | colon, and kidney cancer. Additional                                     |
|   |         |     |                       |                                        | preferred indications include                                            |
|   |         |     |                       |                                        | melanoma, prostate, lung,                                                |
|   |         |     |                       |                                        | pancreatic, esophageal, stomach,                                         |
|   |         |     |                       |                                        | brain, liver, and urinary cancer.                                        |
|   |         |     |                       |                                        | Highly preferred indications include                                     |
|   |         |     |                       |                                        | lipomas and liposarcomas. Other                                          |
|   |         |     |                       |                                        | preferred indications include benign                                     |
|   |         |     |                       |                                        | dysproliferative disorders and pre-                                      |
|   |         |     |                       |                                        | neoplastic conditions, such as, for                                      |
|   |         |     |                       |                                        | example, hyperplasia, metaplasia,                                        |
|   |         |     |                       |                                        | and/or dysplasia.                                                        |
|   | HACCI17 | 408 | Production of IL-8 by | Assay that measures the production     | Highly preferred indications include                                     |
| 4 |         |     | immune cells (such as | of the chemokine interleukin-8 (IL-8)  | eosinophilia, asthma, allergy,                                           |
|   |         |     | the human EOL-1       | from immune cells (such as the EOL-    | hypersensitivity reactions,                                              |
|   |         |     | eosinophil cells)     | 1 human eosinophil cell line) are well | inflammation, and inflammatory                                           |

| disorders. Additional highly prefrent disorders in the furname and hernatopoietic disorders (e.g., sa secribe below under "Immune Activity", and "Blood Pediated Activity", and "Blood Pediated Dowchers"), unalommune diseases (e.g., rheumandi attritis, systemic lumps explements; Cohn's disease multiple schensis and our adsearched below), immunodefaciencies (e.g., and highly preferred indications also include boosting or propostist diseases (e.g., leaching the propostist diseases (e.g., leaching the blood and developed and or described bloods and or as described bloods and or a described bloods and or all and the boosting on costopial-arediated immune response, and suppressing an even pull-produced. | allegy, sethun, and rhinitis, allegy, sethun, and rhinitis, additional preferred indications include microtion (e.g., un infections disease as described nelwor under influenton Bosses), and influentons bisses, and influentation and influentation and influentation and influentation and control include blood diseased set, set described below under "Immune described below under "Immune described below under "Immune described blooders," include blood diseased belonted Diseased Related Diseased Set (Bareful Diseased (Bareful Diseased Set (Bareful Diseased (Bareful Diseased Set (Bareful Diseas |
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| known in the art (for example, measuremen of Le production by PMAT) and may be used or routinely modified to assay the ability of polypeptides of the invention of cheduling antibodies and agoniss or anagoniss of the invention to mount of the public state of immune cell important in altegic responses, they are recruited in studies that the public state of immune cell important in altegic responses, they are recruited in states and modified the inflammony responses of late stage immunementalistic and may have a immunementalistic and may have a immunohelistical diseases and distorters (such as allergy and asthma).                                                                                                                                                                                                                                                                                                                                              | this reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and cells has been linked to cytokine and the chemble in pottlation. Assays for the activation of transcription the activation of transcription the activation of transcription the activation of transcription and may be used or routinely and may be used or routinely ophypeptides of the invention polypeptides of the invention of transcriptions and agoniss or definite analysis of the invention of uniquousless of the  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | transcription through<br>CATA-3 response<br>clerract in immune<br>cells (such as mast<br>cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 408                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HACCII7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis    | and/or as described below) and      | immunodeficiencies (e.g., as      | described below). Preferred     | indications include neoplastic       | diseases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary    | tract cancers and/or as described     | below under "Hyperproliferative    | Disorders"). Other preferred    | indications include benign | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | thrombocytopenia, leukemias,       | Hodgkin's disease, acute            | lymphocytic anemia (ALL),           | plasmacytomas, multiple myeloma,     | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, sepsis, neutropenia,   | neutrophilia, psoriasis, suppression   | of immune reactions to transplanted | organs and tissues, hemophilia,            | hypercoagulation, diabetes mellitus, | endocarditis, meningitis, and Lyme  | Disease.                         |                                     |                                    |                                  |                                  |
|--------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------------|--------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------|
| regulate GATA3 transcription factors | and modulate expression of mast cell | genes important for immune response | development. Exemplary assays for | transcription through the GATA3 | response element that may be used or | routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its    | entirety. Mast cells that may be used | according to these assays are publicly | available (e.g., through the        | ATCC <sup>TM</sup> ). Exemplary human mast | cells that may be used according to  | these assays include the HMC-1 cell | line, which is an immature human | mast cell line established from the | peripheral blood of a patient with | mast cell leukemia, and exhibits | many characteristics of immature |
|                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |                                    |                                  |                                  |
|                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |                                    |                                  |                                  |
|                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |                                    |                                  |                                  |

| Activation of Intrascription Intrascription Intrascription Intrascription Intrascription Interest in Intrascription Interest in Intrascription Interest in Interes                   | 0.00    |     |                       | mast cells.                           |                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----|-----------------------|---------------------------------------|----------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HACCII7 | 408 | Activation of         | This reporter assay measures          | Highly preferred indications include   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |     | transcription through | activation of the NFA1 signaling      | allergy, asthma, and rhinitis.         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |     | NFAT response         | pathway in HMC-1 human mast cell      | Additional preferred indications       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |     | element in immune     | line. Activation of NFAT in mast      | include infection (e.g., an infectious |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |     | cells (such as mast   | cells has been linked to cytokine and | disease as described below under       |
| through the activation of tran through the blackeric charter of Tesls (N) chemen are well-know chemen are well-kno                   |         |     | cells).               | chemokine production. Assays for      | "Infectious Disease"), and             |
| Activated T cells (NI chrough the Naclear)  Activated T cells (NI chromatics of the Immodified to sesses the polypeptides of the information and may be used or T cells (Indulting authorities of the Immodified to see the Immodified to see the Immodified to the Immo                   |         |     |                       | the activation of transcription       | inflammation and inflammatory          |
| chermen are well-known characters are modified to seases the immunost are managemists of the interaction in terraction in terraction through interactions. Exempliar interaction through interaction through interaction through interaction through interaction through interactions. Exempliar interaction through interactions. Exempliar interaction through interaction and Med. (chickling) in the characters and Med. (1999), Alt et al., 1, 1 (1999), Alt et al., 1,                   |         |     |                       | through the Nuclear Factor of         | disorders. Preferred indications also  |
| and may be used or modified to assess the polyopetities of the in foodby-griftes of the in foodby-griftes of the in foodby-griftes of the in antigonists of the in antigonists of the in the interpretation of the interpret                   |         |     |                       | Activated T cells (NFAT) response     | include blood disorders (e.g., as      |
| madified to sesses in modified to sesses of the modified to sesses in modified to sesses in freeholding antibodies of the in freeholding antibodies and produced to the interpretation of the interpre                   |         |     |                       | element are well-known in the art     | described below under "Immune          |
| modified to sesses the polyspeciates of the in- (including unibodiss of the init managemiss of the init managemist of the init managemist managemist exemple transcription through response detented the control of the initial managemists of the init managemists of the init managemists of the initial managemistration of the initial managemists of the initial managemists of the initial managemistration                   |         |     |                       | and may be used or routinely          | Activity", "Blood-Related              |
| (including authorized of the including authorized art the including authorized of the including authorized of the including authorized of the including authorized and including authorized authorized celement and response element and respons                   |         |     |                       | modified to assess the ability of     | Disorders", and/or "Cardiovascular     |
| including authodiss of the including authodiss of the including authodiss of the including authorise of the including authorise of the including increasor include express and modulate express and modulate express increasor inc                   |         |     |                       | polypeptides of the invention         | Disorders"). Preferred indications     |
| randagoniss of the integrated by TA transport regulate by TA Transport involved in immuno                   |         |     |                       | (including antibodies and agonists or | include autoimmune diseases (e.g.,     |
| regulate VRAT trans and modulate express  functions. Exemplain functions. Exemplain functions. Exemplain response element fan response                    |         |     |                       | antagonists of the invention) to      | rheumatoid arthritis, systemic lupus   |
| and modulate express involved in immunon functions. Exemplar functions. Exemplar transcription through response element and response el                   |         |     |                       | regulate NFAT transcription factors   | erythematosis, multiple sclerosis      |
| functions. Exemplar functions. Exemplar functions. Exemplar functions. Exemplar functions. Exemplar functions function function functions function function functions function                   |         |     |                       | and modulate expression of genes      | and/or as described below) and         |
| Intranscription through intranscription through intranscription through in the company of the co                   |         |     |                       | involved in immunomodulatory          | immunodeficiencies (e.g., as           |
| response element in respon                   |         |     |                       | functions. Exemplary assays for       | described below). Preferred            |
| response element in routinely undificial to motituely undificial to motituely undificial to response element are polypeptides of the in (inchuling anthodies) and inchuling anthodies are desired antiquonists of the inseaso afactosed in B Gare 66:1-10 (1998) Malti, Mcthode in E M                   |         |     |                       | transcription through the NFAT        | indications include neoplastic         |
| Continuely mortified in response element and response element and response element and polyperides of the in (including authodies)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |     |                       | response element that may be used or  | diseases (e.g., leukemia, lymphoma,    |
| response demont and response demont and polypoptics of the in anagonists of the in anagonists of the in anagonists of the in anagonists of the in assays distolect in B Gene 66.1-0 (1998) Mahn, Methods in B Mahn, Methods in                   |         |     |                       | routinely modified to test NFAT-      | melanoma, prostate, breast, lung,      |
| Condition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |     |                       | response element activity of          | colon, pancreatic, esophageal,         |
| (including authodiss of the imangonists of the iman                   |         |     |                       | polypeptides of the invention         | stomach, brain, liver, and urinary     |
| The analysis of the first seasons of the first seasons disclosed in B assense disclosed in B and a seasons disclosed in B and a seasons of the first of 10.999, Main. Mathods in B and a seasons of the first of the                    |         |     |                       | (including antibodies and agonists or | tract cancers and/or as described      |
| Sassys distolered in Sassys distolered in Bottle Main, Methods Methods Main, Methods Main, Methods Main, Methods Main, Methods Methods Main, Methods Met                   |         |     |                       | antagonists of the invention) include | below under "Hyperproliferative        |
| Gare 66:1-10 (1998)   Malan, Wichtobes in E.     Cale 66:1-10 (1998)   Per Nutl Acad Scil (1992)     Per Nutl Acad Scil (1992)   Per Nutl Acad Scil (1994)     Cale 10 (1993)   Per Dec Nutl Acad Scil (1994)     Cale 10 (1993)   Per Dec Nutl Acad Scil (1994)     Cale 10 (1993)   Per Dec Nutl Acad Scil (1994)     Cale 10 (1994)   Cale 10 (1994)     Cale                     |         |     |                       | assays disclosed in Berger et al.,    | Disorders"). Other preferred           |
| Malla, Methods in B<br>216:505-366 (1992),<br>216:505-366 (1992),<br>216:505-366 (1992),<br>216:505-366 (1992),<br>216:506 (1992), 216:506 (1992), 216:506 (1993), 216:506<br>(1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1993), 216:506 (1 |         |     |                       | Gene 66:1-10 (1998); Cullen and       | indications include benign             |
| 16.562.58(199); Proco Natl Acad Sci 16. Bubcan Cell Bool Bubcan Cell Bool Bubcan Cell Bool 1(1999); Alit et al., 19 (1999); Alit et al., 19 (1999); Alit et al., 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |     |                       | Malm, Methods in Enzymol              | dysproliferative disorders and pre-    |
| Prov Nat Area Sei Prov Nat Area Sei Prov Nat Area Sei                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |     |                       | 216:362-368 (1992); Henthorn et al.,  | neoplastic conditions, such as, for    |
| 6346 (1988), De Boe<br>Boedem Cell (1999), Alit et al., Ji<br>(1999), Alit et al., Ji<br>(1997), Huterinson and McC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |     |                       | Proc Natl Acad Sci USA 85:6342-       | example, hyperplasia, metaplasia,      |
| Biochem Cell Biol 3   Biochem Cell Biochem Cell Biochem Cell Biol 3   Biochem Cell Bioch                     |         |     |                       | 6346 (1988); De Boer et al., Int J    | and/or dysplasia. Preferred            |
| (1999), Ali et al., J h<br>165(12),7215(2723)<br>Hutchinson and Moc                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |     |                       | Biochem Cell Biol 31(10):1221-1236    | indications include anemia,            |
| 165(12):7215-7223 (<br>Hutchinson and McC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |     |                       | (1999); Ali et al., J Immunol         | pancytopenia, leukopenia,              |
| Hutchinson and McC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |     |                       | 165(12):7215-7223 (2000);             | thrombocytopenia, leukemias,           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |     |                       | Hutchinson and McCloskey, J Biol      | Hodgkin's disease, acute               |

| lymphocytic anemia (ALL), Burkit is Jumphocytic anemia (ALL), Burkit is Jumphoma, arthrifis, AlDS, arthrifis, AlDS, arthrifis, AlDS, arthrifis, AlDS, bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression organis and issues, hemophilia, phyperoogalation, dishetes mellitus, endocartifis, meningitis, and Lyme Disease.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | A highly perferred emboliment of the invention includes a method for their invention includes a method for their and their and their and their production. An attenuate highly perferred emboliment of the studing legs, increasing) IL-5 granding (e.g., increasing) IL-5 granding (e.g., increasing) IL-5 emboliment of the invention and includes a method for stimulating (e.g., increasing) immunoglobulin preferred emboliment of the invention includes a nethod for immunoglobulin preferred emboliment of the invention includes a nethod for immunoglobulin production. A highly perferred includes in immunoglobulin production.  A highly perferred indication includes allegy. A highly preferred allegy. A highly preferred with a highly perferred indication includes allegy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Chem 270/27);16333-16338 (1995), and Tuner et al. 1-5tp Med and Tuner et al. 1-5tp Med and and tuner et al. 1-5tp Med and tuner mest conting to these assays are publicly available (e.g., though the available (e.g., though the available (e.g., though the available (e.g., though the available the HMC-1 cell line, which is an immature human et old line established from the peripheral blood of a putent with must cell lice established from the peripheral blood of a putent with must cell letternia, and exhibits | Les PMAT. Assays for munumonodalatory proteins secreted PAT TEQ cells, must cells basephils, and evidential must cells basephils, and evidential function and lestil get lestil function and lestil guest or fortunities from the fart and may be used or routinely modified to assess the about the function (including authorities of the invention (including authorities of the invention) to mediate the invention to mediate in manumored line fortunities of the production, modulate Beetli ge production, modulate beetling to edil horization, and more mediate immunet of florable immunet and fortunities of the function of benefities the function of the production, modulate immunet of florable immunet and for sevelative florable immunet of receipting sevelates from the production of the produ |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Production of IL-5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 408                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HACCI17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| the production  The first and | the production of cytokines, such as rhinitis. An additional highly preferred indication is infection (e.g. cosinophil function and B cell [g an infectious disease as described production. Such assays that may be below under "Infectious Diseases"), used or contribety modified to less and inflammation and inflammatory moderness admitted. | unsorders. include blood described belo Activity." "Bl Disorders", an Disorders", pr include autoin rheumatoid arr | 5 (1998);<br>or ri et al.,<br>of I Pt<br>ing et al.,<br>of the control of the | disclosed breating or otherwise from an innumerated and are a truman for the are primary from the are than a foreign and the are than a foreign and foreign and foreign and foreign and foreign and a foreign and foreign and foreign and foreign and foreign and precedent indications include being the arms of |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | the productic IL-5, and the Costinophil it production: used or routi                                                                                                                                                                                                                                                                               | numentorino polytypeptides (including at antegoniss (s de assays di Bannol 204 (1999) 21/Juphtocyt                 | Chapter 6.13  Jung et al., 19  25(8):241;25  Z5(8):241;25             | be isolated using the be isolated using disclosed between or the mean human lymphocya may be the thymus and expression of the thymus and expression of the properties of the media mediated immunic mediated immunic mediated in mediated immunic responsiveness to responsiveness to immunomedulated                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|   |         |     |                         |                                         | 3                                      |
|---|---------|-----|-------------------------|-----------------------------------------|----------------------------------------|
|   |         |     |                         |                                         | piasmacytomas, munipie myeroma,        |
|   |         |     |                         |                                         | granulomatous disease, inflammatory    |
|   |         |     |                         |                                         | bowel disease, sepsis, neutropenia,    |
|   |         |     |                         |                                         | neutrophilia, psoriasis, immune        |
|   |         |     |                         |                                         | reactions to transplanted organs and   |
|   |         |     |                         |                                         | tissues, hemophilia,                   |
|   |         |     |                         |                                         | hypercoagulation, diabetes mellitus,   |
|   |         |     |                         |                                         | endocarditis, meningitis, and Lyme     |
|   |         |     |                         |                                         | Disease.                               |
|   | HACCI17 | 408 | Production of ICAM in   | Endothelial cells, which are cells that | Highly preferred indications include   |
| 4 |         |     | endothelial cells (such | line blood vessels, and are involved    | inflammation (acute and chronic),      |
|   |         |     | as human umbilical      | in functions that include, but are not  | restnosis, atheroselerosis, asthma and |
|   |         |     | vein endothelial cells  | limited to, angiogenesis, vascular      | allergy. Highly preferred indications  |
|   |         |     | (HUVEC))                | permeability, vascular tone, and        | include inflammation and               |
|   |         |     |                         | immune cell extravasation.              | inflammatory disorders,                |
|   |         |     |                         | Exemplary endothelial cells that may    | immunological disorders, neoplastic    |
|   |         |     |                         | be used in ICAM production assays       | disorders (e.g. cancer/tumorigenesis), |
|   |         |     |                         | include human umbilical vein            | and cardiovascular disorders (such as  |
|   |         |     |                         | endothelial cells (HUVEC), and are      | described below under "Immune          |
|   |         |     |                         | available from commercial sources.      | Activity", "Blood-Related              |
|   |         |     |                         | The expression of ICAM (CD54),a         | Disorders", "Hyperproliferative        |
|   |         |     |                         | intergral membrane protein, can be      | Disorders" and/or "Cardiovascular      |
|   |         |     |                         | upregulated by cytokines or other       | Disorders"). Highly preferred          |
|   |         |     |                         | factors, and ICAM expression is         | indications include neoplasms and      |
|   |         |     |                         | important in mediating immune and       | cancers such as, for example,          |
|   |         |     |                         | endothelial cell interactions leading   | leukemia, lymphoma, melanoma,          |
|   |         |     |                         | to immune and inflammatory              | renal cell carcinoma, and prostate,    |
|   |         |     |                         | responses. Assays for measuring         | breast, lung, colon, pancreatic,       |
|   |         |     |                         | expression of ICAM-1 are well-          | esophageal, stomach, brain, liver and  |
|   |         |     |                         | known in the art and may be used or     | urinary cancer. Other preferred        |
|   |         |     |                         | routinely modified to assess the        | indications include benign             |
|   |         |     |                         | ability of polypeptides of the          | dysproliferative disorders and pre-    |
|   |         |     |                         | invention (including antibodies and     | neoplastic conditions, such as, for    |
|   |         |     |                         | agonists or antagonists of the          | example, hyperplasia, metaplasia,      |
|   |         |     |                         | invention) to regulate ICAM-1           | and/or dysplasia.                      |
|   |         |     |                         | expression. Exemplary assays that       |                                        |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | immunological and inflammatory distributed inflations included inflammatory distributed (e.g., e.g., e |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| may be used or routinely modified to<br>massure (CAM-1 expression include<br>assays disclosed in: Rolife Bir, et al.,<br>thrensedensis, 149(1).99-110<br>(2000); Panettier RA Jr, et al., J<br>mannanol. 154(5).258-2365 (1995);<br>and, Gransein MA; et al., Am J<br>Physiol Lung Cell Mol Physiol.<br>Physiol Lung Cell Mol Physiol.<br>Physiol Lung Cell Mol Physiol,<br>condens of each of which is lacent<br>in proporated by reference in its<br>entirety. | are well known in the art and may be are well known in the art and may be art or routinely and effect to assess the shilty of polypetides of the shilty of polypetides of the shilty of polypetides of the agencies or antagonists of the art of the polypetide and agonists or antagonists of the carnotto in ordering artibodies and agonists or antagonists of the carnotto in organists of the shilty of polypetides of the carnotto in organists of the ability of polypetides of the ability of  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Abortion of LL-8 by Potaction  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 800                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HACCI17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| resulting from septic shock), restnosis and atherosclensis.                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| in the initiation and perpetuation of inflammation and secretion of IL-8 may play an important role in recuriment and activation of immune cells such as neutrophils, and ymphocytes, and tymphocytes, | RAMPTES FMATT Assays for immunemodulatory profests that induce chemotries of Teels.  Robotoges, and considerable that the state of the |
|                                                                                                                                                                                                        | Production of RANTES (such as braman mubilical vein each of the condition of the condontesial vein (HUVEC))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                        | 408                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                        | HACCI17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                        | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| ruccial indications include benign controlled benign on VCAM dyspouliterative disorders and pressociated neophastic conditions, such as, for morphastic conditions, such as, for tack by accorange, hyperplasia, metaplasia, restands and or dyspitasia. metaplasia, accample, hyperplasia, metaplasia, sa and ofter a such of drawsalis; and other draws | A highly preferred indication is in the art and diabetes melliums are mellium and pulpy preferred andication preprides of indivious lightly preferred indication preprides of its complication asserted with diabetes (e.g., diabetic retinopathy, lines of the finest of the pulpy preferred indication from the finest of the finest o |
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| are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokinss or other factors, and contributes to the vertex-assorian fyriphocytes, fleucocytes and other immune cells from Dlood, versels, thus VCAM expression plays a role in promoding immune and inflammatory responsas.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Simulation of insulin asseys for measuring secretion of pancearic bear oalls.  pancearic bear oalls.  pancearic bear oalls.  part be used or notnicely modified to assess the sality of phycpridises of the invention (including antibodies and againsts or antiagonists or the invention) to estimate it main securion. For example, itsulin securion is measured by PMAT using anti-art natural antial antibodies. Itsulin securion is measured by PMAT using anti-art natural antibodies. Itsulin securion from panceatic does a lissing measured by PMAT using anti-art natural antibodies. Itsulin securion from panceatic does a lissing anti-art natural antibodies. Itsulin securion from panceatic does and also by certain protein/speptides, and also by certain protein/speptides, and also by certain protein/speptides and dishops of the invention (from panceatic cells) by physphides of the invention (including antibodies and agonisis or attainland or final physiol. 271(H p. 2), 2379, 937, 64 al., FFIRS Lett, 377(2), 237, 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HAGAQ26 409                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ٧٠                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|   |         |     |                                                                                             | Logys and Murginis Set al.  Journal of Biomolecular Secreting  19,2-204 (1993) the contents of  each of which is breen incorporated  by reference in its entirety  wetwence cells that may be used  econflig to these seasys are publicly  according to these seasys are publicly  madre may be routinely generated.                                                                                                                                                                                                                                                                                     | The directive Diseases' section below), neuropsity, vision below), neuropsity, vision may be a comparable to the property of t |
|---|---------|-----|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |         |     |                                                                                             | to the doctoring to these usays<br>include an INS-L cells. INS-L cells.<br>were a senti-adherent cell line essablished from cells isolated from<br>an X-ray induced net transplamable<br>and an administrative cells isolated from<br>an X-ray induced net transplamable<br>and a surface of the second from<br>the administrative cells reading<br>characteristics typical of native<br>paracturic bear cells including<br>gluoses inducible insulin secretion.<br>Effectiveness 1481 and et al.                                                                                                        | connecture). An additional highly preferred indication is obesity and/or complications associated with onests. Additional highly preferred indications include weight loss or indications include weight loss or additionally highly preferred indications are complications are sensitived with instillin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| v | HAGDS35 | 410 | Regulation of macastronia and parachies and parachies and pre-adipocytes and pre-adipocytes | Assays for the regulation of measuring the DMEH in seasons of the death the DMEH in seasons element are well-down in response element are well-down in modified to assess the ability of puppeduke of the invention (including anabodies and agoniss or auragoniss of the invention) to activate the DMEH response element in a reporter construct (such as the containing the GLUT4 promoter) and to regulate installing promoter) and to regulate installing promoter) and the publies response element is present in the GLUT4 promotery and though the DMEH response element is present in the GLUT4 | A highly preferred Indication is<br>disheres mellins. Additional highly<br>preferred indications include<br>preferred indications include<br>organization of the properties of the<br>disheres (e.g., dishedir retinopathy,<br>dishedir enphosphaty, kidney diseases<br>(e.g., renal failure, nephropathy,<br>indications of the properties of the<br>and/or other diseases and disorders as<br>section belowly, dishedir neuropathy,<br>and of albedir neuropathy,<br>(e.g., due to dishedir neuropathy,<br>stroke, impotence (e.g., due to<br>stroke, impotence (e.g., due to<br>stroke, impotence (e.g., due to<br>stroke, impotence (e.g., due to<br>chiedic neuropathy, or blood vessel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| _                                     |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |
|---------------------------------------|----------------------------------|-------------------------------------|-------------------------------|---------------------------------------|-------------------------------------|-------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|----------------------------------------|------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------|-----------------------------|----------------------------------------|--------------------------------------|------------------------------------|----------------------------------|---------------------------------------|------------------------------------|
| confusion, drowsiness, nonketotic     | hyperglycemic-hyperosmolar coma. | cardiovascular disease (e.g., heart | disease, atherosclerosis,     | microvascular disease, hypertension,  | stroke, and other diseases and      | disorders as described in the | "Cardiovascular Disorders" section  | below), dyslipidemia, endocrine     | disorders (as described in the     | "Endocrine Disorders" section       | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious      | Discases" section below, especially | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications    | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly preferred | indications are complications  | associated with insulin resistance. |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |
| transcription factor that is required | for insulin regulation of Glut4  | expression in skeletal muscle.      | GLUT4 is the primary insulin- | responsive glucose transporter in fat | and muscle tissue. Exemplary assays | that may be used or routinely | modified to test for DMEF1 response | element activity (in adipocytes and | pre-adipocytes) by polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed    | inThai, M.V., et al., J Biol Chem,  | 273(23):14285-92 (1998); Mora, S.,  | et al., J Biol Chem, 275(21):16323-8 | (2000); Liu, M.L., et al., J Biol | Chem, 269(45):28514-21 (1994);      | "Identification of a 30-base pair  | regulatory element and novel DNA       | binding protein that regulates the | human GLUT4 promoter in             | transgenic mice", J Biol Chem. 2000  | Aug 4;275(31):23666-73; Berger, et   | al., Gene 66:1-10 (1988); and,    | Cullen, B., et al., Methods in | Enzymol. 216:362-368 (1992), the    | contents of each of which is herein | incorporated by reference in its | entirety. Adipocytes and pre- | adipocytes that may be used | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary cells that may be used | according to these assays include the | mouse 3T3-L1 cell line which is an |
|                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |
|                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       | _                                  |
|                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |

|                                                                                                                                                                                                                                                                                                   | A highly preferred emboliment of the invention includes a method profileration, An alternative highly profileration, An alternative highly preferred emboliment of the invention includes a method for including adiposyte proliferation inhibiting adiposyte proliferation A highly preferred emboliment of the invention includes a method for includes a method for inhibiting and procyce differentiation. A highly preferred emboliment of the instruction includes as method for simulating (e.g., increasing) assumption to An alternative highly preferred emboliment of the inhibiting the activation of (e.g., highly preferred emboliment of the inhibiting the activation of (e.g., the adiacontain studies of metalvising adiposytes. Highly preferred inhibiting the activation of e.g., as described below the metal proferred indications side interesting indications is shown Highly preferred indications is shown Highly preferred indications is shown Highly preferred indications is shown that is a method for indications is shown that is a method for indications is shown that is a method for indications is shown that the preferred indications is shown that is a method for indications is shown that is a method for indication is shown that is a method for indication is shown that is a method for the shown that is a method for indication is |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| adherent mouse preadipocyte cell line. Mouse 271-L cells are a continuous substant of 373 line bolds developed through cloud isolation. These cells undergo a pre- adipocyte to adpose-like conversion adipocyte to adpose-like conversion culture apporpiate differentiation culture conditions. | coxumple an II-lk Limes easay, for<br>filters easay, Kinken seasy, for<br>the Ray and mandaction that regulate<br>cell position and the season and<br>we well known in the ear and may be<br>used or routinely modified to assess<br>the childs of polypophides of the<br>invention of including anthodics and<br>againsts or antagonies of the<br>invention of proteing anthodics and<br>againsts or antagonies of the<br>profileration, activation, and<br>enterion) to promote or infinite cell<br>profileration, activation, and<br>filteration activation, and<br>the RK kiness activity that may be used<br>RK kiness activity that may be used<br>the mortal publicate of the invention included<br>the mortal publicates and agonies or<br>mangionis of the invention include<br>the assays dasclosed in Forter et al.,<br>(1998), Le Marchand-Brastel Y. Exp.<br>(1998), Le outenties of<br>each of which are beerin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                   | Adriguest of Adriguest of Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                   | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                   | Нлате                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| described below under "Hyperproliferative Disorders"). Profermed indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel blockage heart disease stroke          | impotence and/or as described below | under "Innnune Activity",          | "Blood-Related Disorders", immune                                         | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | indi | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, |
|--------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------|-------------------------------------|------------------------------------|---------------------------------------------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|------|----------------------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|
| incorporated by reference in its entirety. Mouse adipocyte cells that                      | assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ). Exemplary mouse adinocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cen<br>line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |      |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |
|                                                                                            |                                      |                                                                               |                                     |                                    |                                                                           |                                     |                                      |                                     |                              |                                     |                                     |                              |      |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |
|                                                                                            |                                      |                                                                               |                                     |                                    |                                                                           |                                     |                                      |                                     |                              |                                     |                                     |                              |      |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |
|                                                                                            |                                      |                                                                               |                                     |                                    |                                                                           |                                     |                                      |                                     |                              |                                     |                                     |                              |      |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |

|   |  | microvascular disease hynertension      |
|---|--|-----------------------------------------|
|   |  | ottolio and other discount and          |
| _ |  | SUOKE, and other diseases and           |
|   |  | disorders as described in the           |
| _ |  | "Cardiovascular Disorders" section      |
| _ |  | below), dyslipidemia, endocrine         |
| _ |  | disorders (as described in the          |
| _ |  | "Endocrine Disorders" section           |
|   |  | below), neuropathy, vision              |
|   |  | impairment (e.g., diabetic retinopathy  |
|   |  | and blindness), ulcers and impaired     |
|   |  | wound healing, infection (e.g.,         |
|   |  | infectious diseases and disorders as    |
|   |  | described in the "Infectious            |
|   |  | Diseases" section below (particularly   |
| _ |  | of the urinary tract and skin). An      |
|   |  | additional highly preferred indication  |
|   |  | is obesity and/or complications         |
|   |  | associated with obesity. Additional     |
|   |  | highly preferred indications include    |
|   |  | weight loss or alternatively, weight    |
|   |  | gain. Additional highly                 |
| _ |  | preferred indications are               |
|   |  | complications associated with insulin   |
|   |  | resistance. Additional highly           |
|   |  | preferred indications are disorders of  |
|   |  | the musculoskeletal systems             |
|   |  | including myopathies, muscular          |
|   |  | dystrophy, and/or as described          |
| _ |  | herein. Additional highly               |
|   |  | preferred indications include,          |
|   |  | hypertension, coronary artery           |
| _ |  | disease, dyslipidemia, gallstones,      |
|   |  | osteoarthritis, degenerative arthritis, |
|   |  | eating disorders, fibrosis, cachexia,   |
|   |  | and kidney diseases or disorders.       |
| _ |  | Preferred indications include           |
|   |  | neoplasms and cancer, such as,          |

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| Chang and Karin Nature                      | disorders (e.g. as described helow     |
|---------------------------------------------|----------------------------------------|
| 410(6824):37-40 (2001); and Cobb            | under "Endocrine Disorders").          |
| MH, Prog Biophys Mol Biol 71(3-             | Highly preferred indications also      |
| 4):479-500 (1999); the contents of          | include neoplastic diseases (e.g.,     |
| each of which are herein                    | lipomas, liposarcomas, and/or as       |
| incorporated by reference in its            | described below under                  |
| entirety. Mouse adipocyte cells that        | "Hyperproliferative Disorders").       |
| may be used according to these              | Preferred indications include blood    |
| assays are publicly available (e.g.,        | disorders (e.g., hypertension,         |
| through the ATCC <sup>TM</sup> ). Exemplary | congestive heart failure, blood vessel |
| mouse adipocyte cells that may be           | blockage, heart disease, stroke,       |
| used according to these assays              | impotence and/or as described below    |
| include 3T3-L1 cells. 3T3-L1 is an          | under "Immune Activity",               |
| adherent mouse preadipocyte cell            | "Cardiovascular Disorders", and/or     |
| line that is a continuous substrain of      | "Blood-Related Disorders"), immune     |
| 3T3 fibroblast cells developed              | disorders (e.g., as described below    |
| through clonal isolation and undergo        | under "Immune Activity"), neural       |
| a pre-adipocyte to adipose-like             | disorders (e.g., as described below    |
| conversion under appropriate                | under "Neural Activity and             |
| differentiation conditions known in         | Neurological Diseases"), and           |
| the art.                                    | infection (e.g., as described below    |
|                                             | under "Infectious Disease").           |
|                                             | A highly preferred indication is       |
|                                             | diabetes mellitus. An additional       |
|                                             | highly preferred indication is a       |
|                                             | complication associated with           |
|                                             | diabetes (e.g., diabetic retinopathy,  |
|                                             | diabetic nephropathy, kidney disease   |
|                                             | (e.g., renal failure, nephropathy      |
|                                             | and/or other diseases and disorders as |
|                                             | described in the "Renal Disorders"     |
|                                             | section below), diabetic neuropathy,   |
|                                             | nerve disease and nerve damage         |
|                                             | (e.g., due to diabetic neuropathy),    |
|                                             | blood vessel blockage, heart disease,  |
|                                             | stroke, impotence (e.g., due to        |
|                                             | diabetic neuropathy or blood vessel    |

|  | blockage) seizmes mental               |
|--|----------------------------------------|
|  | COCCAGE, SCIZING, INCHINA              |
|  | confusion, growsiness, nonketone       |
|  | hyperglycemic-hyperosmolar coma,       |
|  | cardiovascular disease (e.g., heart    |
|  | disease, atherosclerosis,              |
|  | microvascular disease, hypertension,   |
|  | stroke, and other diseases and         |
|  | disorders as described in the          |
|  | "Cardiovascular Disorders" section     |
|  | below), dyslipidemia, endocrine        |
|  | disorders (as described in the         |
|  | "Endocrine Disorders" section          |
|  | below), neuropathy, vision             |
|  | impairment (e.g., diabetic retinopathy |
|  | and blindness), ulcers and impaired    |
|  | wound healing, infection (e.g.,        |
|  | infectious diseases and disorders as   |
|  | described in the "Infectious           |
|  | Diseases" section below (particularly  |
|  | of the urinary tract and skin). An     |
|  | additional highly preferred indication |
|  | is obesity and/or complications        |
|  | associated with obesity. Additional    |
|  | highly preferred indications include   |
|  | t los                                  |
|  | gain. Additional highly                |
|  | preferred indications are              |
|  | complications associated with insulin  |
|  | resistance. Additional highly          |
|  | preferred indications are disorders of |
|  | the musculoskeletal systems            |
|  | including myopathies, muscular         |
|  | dystrophy, and/or as described         |
|  | herein. Additional highly              |
|  | preferred indications include,         |
|  | hypertension, coronary artery          |
|  | disease, dyslipidemia, gallstones,     |

| Addition through transarption through the cAMP response response element are well-known in a calculation through the cAMP response response element are well-known in associated with clear and may be used or rountinely highly perferred indications include adipocytes.  Indicating authorics and the invention of indication sinches mediation of increase cAMP, regulate CREB in the invention of increase cAMP, regulate CREB in the invention of increase cAMP, regulate CREB in care and indication is diabete include in the interaction of increase cAMP, regulate CREB in care and including authorics and agonism of indication is diabete include in the interaction of increase cAMP, regulate CREB in care and including authorics and agonism of the interaction is diabete included in the interaction of increase cAMP, regulate CREB increase included in its acomplication associated with diabete of explicit elements. In the active the interportation in the Please of the interference in the Please and in the Please of indication into without other (example, a) alternative of the interport of the inte |
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| <u>14</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 9.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| HAHDB16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|   |         |     |                    | transcription factor CREB (CRE           | diabetic neuropathy or blood wessel    |
|---|---------|-----|--------------------|------------------------------------------|----------------------------------------|
|   |         |     |                    | hinding protein) Exemplary assays        | blockage) seizures mental              |
|   |         |     |                    | for transcription through the cAMP       | confusion, drowsiness, nonketotic      |
|   |         |     |                    | response element that may be used or     | hyperglycemic-hyperosmolar coma,       |
|   |         |     |                    | routinely modified to test cAMP-         | cardiovascular disease (e.g., heart    |
|   |         |     |                    | response element activity of             | disease, atherosclerosis,              |
|   |         |     |                    | polypeptides of the invention            | microvascular disease, hypertension,   |
|   |         |     |                    | (including antibodies and agonists or    | stroke, and other diseases and         |
|   |         |     |                    | antagonists of the invention) include    | disorders as described in the          |
|   |         |     |                    | assays disclosed in Berger et al.,       | "Cardiovascular Disorders" section     |
|   |         |     |                    | Gene 66:1-10 (1998); Cullen and          | below), dyslipidemia, endocrine        |
|   |         |     |                    | Malm, Methods in Enzymol                 | disorders (as described in the         |
|   |         |     |                    | 216:362-368 (1992); Henthorn et al.,     | "Endocrine Disorders" section          |
|   |         |     |                    | Proc Natl Acad Sci USA 85:6342-          | below), neuropathy, vision             |
|   |         |     |                    | 6346 (1988); Reusch et al., Mol Cell     | impairment (e.g., diabetic retinopathy |
|   |         |     |                    | Biol 20(3):1008-1020 (2000); and         | and blindness), ulcers and impaired    |
|   |         |     |                    | Klemm et al., J Biol Chem 273:917-       | wound healing, and infection (e.g.,    |
|   |         |     |                    | 923 (1998), the contents of each of      | infectious diseases and disorders as   |
|   |         |     |                    | which are herein incorporated by         | described in the "Infectious           |
|   |         |     |                    | reference in its entirety. Pre-          | Diseases" section below, especially    |
|   |         |     |                    | adipocytes that may be used              | of the urinary tract and skin), carpal |
|   |         |     |                    | according to these assays are publicly   | tunnel syndrome and Dupuytren's        |
|   |         |     |                    | available (e.g., through the ATCCTM)     | contracture). Additional highly        |
|   |         |     |                    | and/or may be routinely generated.       | preferred indications are              |
|   |         |     |                    | Exemplary mouse adipocyte cells          | complications associated with insulin  |
|   |         |     |                    | that may be used according to these      | resistance.                            |
|   |         |     |                    | assays include 3T3-L1 cells. 3T3-L1      |                                        |
|   |         |     |                    | is an adherent mouse preadipocyte        |                                        |
|   |         |     |                    | cell line that is a continuous substrain |                                        |
|   |         |     |                    | of 3T3 fibroblast cells developed        |                                        |
|   |         |     |                    | through clonal isolation and undergo     |                                        |
|   |         |     |                    | a pre-adipocyte to adipose-like          |                                        |
|   |         |     |                    | conversion under appropriate             |                                        |
|   |         |     |                    | differentiation conditions known in      |                                        |
|   |         |     |                    | the art.                                 |                                        |
|   | HAHDB16 | 412 | Production of      | IFNgamma FMAT. IFNg plays a              | A highly preferred embodiment          |
| 8 |         |     | IFNgamma using a T | central role in the immune system        | of the invention includes a method     |
|   |         |     |                    |                                          |                                        |

| cells | and is considered to be a             | for stimulating the production of      |
|-------|---------------------------------------|----------------------------------------|
|       | promittanimatory cytokine. IF Ng      | IFNg. An alternative highly preferred  |
|       | differentiation: promotec Inff2 and   | includes a method for inhibiting the   |
|       | inhibits 19E secretion: induces       | production of TFNg. Highly             |
|       | macrophage activation; and increases  | incl                                   |
|       | MHC expression. Assays for            | disorders (e.g., as described below    |
|       | immunomodulatory proteins             | under "Immune Activity", "Blood-       |
|       | produced by T cells and NK cells      | Related Disorders", and/or             |
|       | that regulate a variety of            | "Cardiovascular Disorders"), and       |
|       | inflammatory activities and inhibit   | infection (e.g., viral infections,     |
|       | TH2 helper cell functions are well    | tuberculosis, infections associated    |
|       | known in the art and may be used or   | with chronic granulomatosus disease    |
|       | routinely modified to assess the      | and malignant osteoporosis, and/or as  |
|       | ability of polypeptides of the        | described below under "Infectious      |
|       | invention (including antibodies and   | Disease"). Highly preferred            |
|       | agonists or antagonists of the        | indications include autoimmune         |
|       | invention) to mediate                 | disease (e.g., rheumatoid arthritis,   |
|       | immunomodulation, regulate            | systemic lupus erythematosis,          |
|       | inflammatory activities, modulate     | multiple sclerosis and/or as described |
|       | TH2 helper cell function, and/or      | below), immunodeficiency (e.g., as     |
|       | mediate humoral or cell-mediated      | described below), boosting a T cell-   |
|       | immunity. Exemplary assays that       | mediated immune response, and          |
|       | test for immunomodulatory proteins    | suppressing a T cell-mediated          |
|       | evaluate the production of cytokines, | immune response. Additional highly     |
|       | such as Interferon gamma (IFNg),      | preferred indications include          |
|       | and the activation of T cells. Such   | inflammation and inflammatory          |
|       | assays that may be used or routinely  | disorders. Additional preferred        |
|       | modified to test immunomodulatory     | indications include idiopathic         |
|       | activity of polypeptides of the       | pulmonary fibrosis. Highly             |
|       | invention (including antibodies and   | preferred indications include          |
|       | agonists or antagonists of the        | neoplastic diseases (e.g., leukemia,   |
|       | invention) include the assays         | lymphoma, melanoma, and/or as          |
|       | disclosed in Miraglia et al., J       | described below under                  |
|       | Biomolecular Screening 4:193-204      | "Hyperproliferative Disorders").       |
|       | (1999); Rowland et al.,               | Highly preferred indications include   |
|       | "Lymphocytes: a practical approach"   | neoplasms and cancers, such as, for    |

|   |         |     |                      | Chapter 6:138-160 (2000); Gonzalez    | example, leukenna, lymphoma,          |
|---|---------|-----|----------------------|---------------------------------------|---------------------------------------|
|   |         |     |                      | et al., J Clin Lab Anal 8(5):225-233  | melanoma, and prostate, breast, lung, |
|   |         |     |                      | (1995); Billiau et al., Ann NY Acad   | colon, pancreatic, esophageal,        |
|   |         |     |                      | Sci 856:22-32 (1998); Boehm et al.,   | stomach, brain, liver and urinary     |
|   |         |     |                      | Annu Rev Immunol 15:749-795           | cancer. Other preferred indications   |
|   |         |     |                      | (1997), and Rheumatology (Oxford)     | include benign dysproliferative       |
|   |         |     |                      | 38(3):214-20 (1999), the contents of  | disorders and pre-neoplastic          |
|   |         |     |                      | each of which are herein              | conditions, such as, for example,     |
|   |         |     |                      | incorporated by reference in its      | hyperplasia, metaplasia, and/or       |
|   |         |     |                      | entirety. Human T cells that may be   | dysplasia. Preferred indications      |
|   |         |     |                      | used according to these assays may    | include anemia, pancytopenia,         |
|   |         |     |                      | be isolated using techniques          | leukopenia, thrombocytopenia,         |
|   |         |     |                      | disclosed herein or otherwise known   | Hodgkin's disease, acute              |
|   |         |     |                      | in the art. Human T cells are primary | lymphocytic anemia (ALL),             |
|   |         |     |                      | human lymphocytes that mature in      | plasmacytomas, multiple myeloma,      |
|   |         |     |                      | the thymus and express a T Cell       | Burkitt's lymphoma, arthritis, AIDS,  |
|   |         |     |                      | receptor and CD3, CD4, or CD8.        | granulomatous disease, inflammatory   |
|   |         |     |                      | These cells mediate humoral or cell-  | bowel disease, sepsis, neutropenia,   |
|   |         |     |                      | mediated immunity and may be          | neutrophilia, psoriasis, suppression  |
|   |         |     |                      | preactivated to enhance               | of immune reactions to transplanted   |
|   |         |     |                      | responsiveness to                     | organs and tissues, hemophilia,       |
|   |         |     |                      | immunomodulatory factors.             | hypercoagulation, diabetes mellitus,  |
|   |         |     |                      |                                       | endocarditis, meningitis, Lyme        |
|   |         |     |                      |                                       | Disease, asthma and allergy.          |
|   | HAICP19 | 413 | Activation of        | Kinase assay. Kinase assays, for      | A highly preferred embodiment of      |
| 6 |         |     | Adipocyte PI3 Kinase | example an GSK-3 assays, for PI3      | the invention includes a method for   |
|   |         |     | Signalling Pathway   | kinase signal transduction that       | increasing adipocyte survival An      |
|   |         |     |                      | regulate glucose metabolism and cell  | alternative highly preferred          |
|   |         |     |                      | survival are well-known in the art    | embodiment of the invention           |
|   |         |     |                      | and may be used or routinely          | includes a method for decreasing      |
|   |         |     |                      | modified to assess the ability of     | adipocyte survival. A preferred       |
|   |         |     |                      | polypeptides of the invention         | embodiment of the invention           |
|   |         |     |                      | (including antibodies and agonists or | includes a method for stimulating     |
|   |         |     |                      | antagonists of the invention) to      | adipocyte proliferation. An           |
|   |         |     |                      | promote or inhibit glucose            | alternative highly preferred          |
|   |         |     |                      | metabolism and cell survival.         | embodiment of the invention           |
|   |         |     |                      | Exemplary assays for PI3 kinase       | includes a method for inhibiting      |

| adipocyte proliferation. A             | preferred embodiment of the         | invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention            | includes a method for inhibiting | adipocyte differentiation. Highly | preferred indications include       | endocrine disorders (e.g., as | described below under "Endocrine     | Disorders"). Preferred indications | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as     | described below under          | "Hyperproliferative Disorders"),     | slood disorders (e.g., hypertension, | congestive heart failure, blood vessel | olockage, heart disease, stroke, | impotence and/or as described below | inder "Immune Activity",         | "Cardiovascular Disorders", and/or    | "Blood-Related Disorders"), immune | disorders (e.g., as described below  | inder "Immune Activity"), neural | disorders (e.g., as described below | under "Neural Activity and          | Neurological Diseases"), and | infection (e.g., as described below | under "Infectious Disease"). A | highly preferred indication is | diabetes mellitus. An | additional highly preferred indication | is a complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy |
|----------------------------------------|-------------------------------------|---------------------------------|----------------------------------------|---------------------------------|----------------------------------------|----------------------------------|-----------------------------------|-------------------------------------|-------------------------------|--------------------------------------|------------------------------------|------------------------------------|--------------------------------------|--------------------------------|--------------------------------------|--------------------------------------|----------------------------------------|----------------------------------|-------------------------------------|----------------------------------|---------------------------------------|------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-------------------------------------|------------------------------|-------------------------------------|--------------------------------|--------------------------------|-----------------------|----------------------------------------|-----------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|
| $\vdash$                               | _                                   |                                 | _                                      | ·                               | _                                      |                                  |                                   | _                                   | _                             |                                      | Disord                             | _                                  |                                      | Ī                              |                                      | _                                    | Ť                                      |                                  | _                                   |                                  | jo ui                                 |                                    | _                                    |                                  | disorde                             | _                                   | Neurol                       | infection                           | under,                         | highly                         | diabete               | additio                                | is a col                          | diabete                               | diabeti                              | (e.g., n                          |
| activity that may be used or routinely | modified to test P13 kinase-induced | activity of polypeptides of the | invention (including antibodies and    | agonists or antagonists of the  | invention) include assays disclosed in | Forrer et al., Biol Chem 379(8-  | 9):1101-1110 (1998); Nikoulina et | al., Diabetes 49(2):263-271 (2000); | and Schreyer et al., Diabetes | 48(8):1662-1666 (1999), the contents | of each of which are herein        | incorporated by reference in its   | entirety. Mouse adipocyte cells that | may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary       | mouse adipocyte cells that may be      | used according to these assays   | include 3T3-L1 cells. 3T3-L1 is an  | adherent mouse preadipocyte cell | line that is a continous substrain of | 3T3 fibroblast cells developed     | through clonal isolation and undergo | a pre-adipocyte to adipose-like  | conversion under appropriate        | differentiation conditions known in | the art.                     |                                     |                                |                                |                       |                                        |                                   |                                       |                                      |                                   |
|                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |                                      |                                   |
|                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |                                      |                                   |
|                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |                                      |                                   |
|                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |                                      |                                   |

|  |          | and/or other diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | 3 77     | The state of the s |
|  | 0        | described in the "Kenal Disorders"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | 8        | section below), diabetic neuropathy,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | <u>u</u> | nerve disease and nerve damage (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | 9        | due to diabetic neuropathy), blood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | ^        | vessel blockage, heart disease,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | s        | stroke, impotence (e.g., due to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | P        | diabetic neuropathy or blood vessel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | -0       | blockage), seizures, mental                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | 9        | confusion, drowsiness, nonketotic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  |          | hyperglycemic-hyperosmolar coma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | 0        | cardiovascular disease (e.g., heart                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | 9        | disease, atherosclerosis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|  |          | microvascular disease, hypertension,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | s        | stroke, and other diseases and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | 9        | disorders as described in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | =        | "Cardiovascular Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  |          | below), dyslipidemia, endocrine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | P        | disorders (as described in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  |          | "Endocrine Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  |          | below), neuropathy, vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | -=       | impairment (e.g., diabetic retinopathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | es       | and blindness), ulcers and impaired                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  |          | wound healing, infection (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | -=-      | infectious diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | P        | described in the "Infectious                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  |          | Diseases" section below, especially                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | 0        | of the urinary tract and skin), carpal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | Δ.       | tunnel syndrome and Dupuytren's                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  |          | contracture). An additional                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  |          | highly preferred indication is obesity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | 65       | and/or complications associated with                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | 0        | obesity. Additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | -=       | indications include weight loss or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | 85       | alternatively, weight gain.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | _        | Additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | ii.      | indications are complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

|   |         |     |                      |                                       | associated with insulin resistance      |
|---|---------|-----|----------------------|---------------------------------------|-----------------------------------------|
|   |         |     |                      |                                       | Additional highly preferred             |
|   |         |     |                      |                                       | indications are disorders of the        |
|   |         |     |                      |                                       | musculoskeletal systems including       |
|   |         |     |                      |                                       | myopathics, muscular dystrophy,         |
|   |         |     |                      |                                       | and/or as described herein.             |
|   |         |     |                      |                                       | Additional highly preferred             |
|   |         |     |                      |                                       | indications include, hypertension,      |
|   |         |     |                      |                                       | coronary artery disease,                |
|   |         |     |                      |                                       | dyslipidemia, gallstones,               |
|   |         |     |                      |                                       | ostcoarthritis, degenerative arthritis, |
|   |         |     |                      |                                       | cating disorders, fibrosis, cachexia,   |
|   |         |     |                      |                                       | and kidney diseases or disorders.       |
|   |         |     |                      |                                       | Highly preferred indications include    |
|   |         |     |                      |                                       | neoplasms and cancer, such as,          |
|   |         |     |                      |                                       | lipoma, liposarcoma, lymphoma,          |
|   |         |     |                      |                                       | leukemia and breast, colon, and         |
|   |         |     |                      |                                       | kidney cancer. Additional highly        |
|   |         |     |                      |                                       | preferred indications include           |
|   |         |     |                      |                                       | melanoma, prostate, lung,               |
|   |         |     |                      |                                       | pancreatic, esophageal, stomach,        |
|   |         |     |                      |                                       | brain, liver, and urinary cancer.       |
|   |         |     |                      |                                       | Other preferred indications include     |
|   |         |     |                      |                                       | benign dysproliferative disorders and   |
|   |         |     |                      |                                       | pre-neoplastic conditions, such as,     |
|   |         |     |                      |                                       | for example, hyperplasia, metaplasia,   |
|   |         |     |                      |                                       | and/or dysplasia.                       |
|   | HAICP19 | 413 | Production of ICAM-1 | Assays for measuring expression of    | Preferred embodiments of the            |
| 6 |         |     |                      | ICAM-1 are well-known in the art      | invention include using polypeptides    |
|   |         |     |                      | and may be used or routinely          | of the invention (or antibodies,        |
|   |         |     |                      | modified to assess the ability of     | agonists, or antagonists thereof) in    |
|   |         |     |                      | polypeptides of the invention         | detection, diagnosis, prevention,       |
|   |         |     |                      | (including antibodies and agonists or | and/or treatment of Vascular Disease,   |
|   |         |     |                      | antagonists of the invention) to      | Atherosclerosis, Restenosis, Stroke,    |
|   |         |     |                      | regulate ICAM-1 expression.           | and Asthma.                             |
|   |         |     |                      | Exemplary assays that may be used     |                                         |
|   |         |     |                      | or routinely modified to measure      |                                         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | allegy, astimut, and rhintis, allegy, astimut, and rhintis, allegy, astimut, and rhintis, additional preferent indications include infection (e.g., an infections include infection (e.g., an infections laces are described below under "Infections Diseases"), and minimute of the control of includes also include blood disorders. Perferend infections also include blood disorders (e.g., as excepted below under "Immune Activity". Blood-Related Activity", Preferred indications include automatune diseases (e.g., rheumanoid arthritis, systemic lupus and/or as described below). Preferred below and arthritis, systemic lupus and/or as described below). Preferred indications and/or as described below). Preferred is described below). Preferred in the control of the contr |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ICAM-1 expression include assays delessed in Roll Bit, et al., Alterosclerosis, 149(1.99-110 Choly Emetter ICA A., et al., Immunol, 145(9.238-236 (1992), Immunol, 145(9.238-238-238), Immunol, 156(9.238-238-238-238-238-238-238-238-238-238- | activation of the NFAT signaling plants are stated to the NFAT signaling plants in the NFAT signaling plants in the NFAT signaling plants in the NFAT in must cell line. Activation of NFAT in must cell misc and organized and organized signaling the NFAT in must chemokine production. Assays for the activation of transacription through the Nivolear Favoro of Activated T cells (NFAT) response former are well-blackown in the art and may be used or routinely oppopping to seed or routinely oppopping of the investion of the designation of the investion of the designation of the investion of conducting authorities and against the NFAT reasonable of geness and annodating expression of genes and modulate expression of genes functions. Exempter assays for functions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | transcription through<br>transcription through<br>AVI response<br>clement in immune<br>celle (such as mast<br>cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 413                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HAICP19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ٥                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|   |         |     |                       | transcription through the NFA1             | indications include neoplastic       |
|---|---------|-----|-----------------------|--------------------------------------------|--------------------------------------|
|   |         |     |                       | response element that may be used or       | discases (e.g., leukemia, lymphoma,  |
|   |         |     |                       | routinely modified to test NFAT-           | melanoma, prostate, breast, lung,    |
|   |         |     |                       | response element activity of               | colon, pancreatic, esophageal,       |
|   |         |     |                       | polypeptides of the invention              | stomach, brain, liver, and urinary   |
|   |         |     |                       | (including antibodies and agonists or      | tract cancers and/or as described    |
|   |         |     |                       | antagonists of the invention) include      | below under "Hyperproliferative      |
|   |         |     |                       | assays disclosed in Berger et al.,         | Disorders"). Other preferred         |
|   |         |     |                       | Gene 66:1-10 (1998); Cullen and            | indications include benign           |
|   |         |     |                       | Malm, Methods in Enzymol                   | dysproliferative disorders and pre-  |
|   |         |     |                       | 216:362-368 (1992); Henthorn et al.,       | neoplastic conditions, such as, for  |
|   |         |     |                       | Proc Natl Acad Sci USA 85:6342-            | example, hyperplasia, metaplasia,    |
|   |         |     |                       | 6346 (1988); De Boer et al., Int J         | and/or dysplasia. Preferred          |
|   |         |     |                       | Biochem Cell Biol 31(10):1221-1236         | indications include anemia,          |
|   |         |     |                       | (1999); Ali et al., J Immunol              | pancytopenia, leukopenia,            |
|   |         |     |                       | 165(12):7215-7223 (2000);                  | thrombocytopenia, leukemias,         |
|   |         |     |                       | Hutchinson and McCloskey, J Biol           | Hodekin's disease, acute             |
|   |         |     |                       | Chem 270(27):16333-16338 (1995),           | lymphocytic anemia (ALL),            |
|   |         |     |                       | and Turner et al., J Exp Med               | plasmacytomas, multiple myeloma,     |
|   |         |     |                       | 188:527-537 (1998), the contents of        | Burkitt's lymphoma, arthritis, AIDS, |
|   |         |     |                       | each of which are herein                   | granulomatous disease, inflammatory  |
|   |         |     |                       | incorporated by reference in its           | bowel disease, sepsis, neutropenia,  |
|   |         |     |                       | entirety. Mast cells that may be used      | neutrophilia, psoriasis, suppression |
|   |         |     |                       | according to these assays are publicly     | of immune reactions to transplanted  |
|   |         |     |                       | available (e.g., through the               | organs and tissues, hemophilia,      |
|   |         |     |                       | ATCC <sup>TM</sup> ). Exemplary human mast | hypercoagulation, diabetes mellitus, |
|   |         |     |                       | cells that may be used according to        | endocarditis, meningitis, and Lyme   |
|   |         |     |                       | these assays include the HMC-1 cell        | Disease.                             |
|   |         |     |                       | line, which is an immature human           |                                      |
|   |         |     |                       | mast cell line established from the        |                                      |
|   |         |     |                       | peripheral blood of a patient with         |                                      |
|   |         |     |                       | mast cell leukemia, and exhibits           |                                      |
|   |         |     |                       | many characteristics of immature           |                                      |
|   |         |     |                       | mast cells.                                |                                      |
|   | HAICP19 | 413 | Activation of Natural | Kinase assay. Kinase assays, for           | A highly preferred embodiment        |
| 6 |         |     | Killer Cell ERK       | example an Elk-1 kinase assay, for         |                                      |
|   |         |     | Signaling Pathway.    | ERK signal transduction that regulate      | for stimulating natural killer cell  |

| proliferation. An alternative highly perferred embodiment of the invention includes a method for invention includes a method for inhibiting neural skiller cell proliferation. A highly preferred modelment of the invention includes a method for stimulating includes a method for stimulating includes a method for stimulating alternative highly preferred alternative highly preferred includes an enchod for inhibiting includes a method for inhibiting includes a method for inhibiting that alternative highly preferred and alternati | neoplastic diseases (e.g., as described<br>below under "Hyperpolitierarie" o<br>Disouters"), blood disorders (e.g., as<br>escelebed below under "Immune<br>Activity", "Cardiovascular<br>Disorders", and/or "Blood-Related<br>Disorders," manue disorders (e.g., as<br>described below under "Immune<br>as described below under "Immune<br>described below under "Immune" | threat broad rankers (e.g., its structure broad rankers) (e.g., its structure) (e.g., its christian) (e.g., it |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cell proliferation or differentiation were Nel known in the art and may be used or reutinely modified to assess the major and the self-self-self-self-self-self-self-self-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | (including antibodies and agonists or<br>amonious of the invention) include<br>the assays disclosed in Forrer et al.,<br>(1989). Expraisis M. Biochem Soc<br>Symp 64:29-48 (1999); Chang and<br>Extra Nature (1989); Chang and<br>Extra Nature (1989); Chang and<br>Chol); and Cobb Mil, Prog Biophys<br>Mol Bio J (164-492-500 (1999);<br>the contents of each of which are<br>their incorporated by reference in<br>a contents of such of their are                                                                                                                            | entury, vastural stitle ceits finat<br>may be used according to these<br>assays are publicly available (e.g.,<br>through the ATCCPA). Exemplary<br>through the ATCCPA). Exemplary<br>according to these assays include the<br>human natural killer cell lines (for<br>example, IM-AT cells which have<br>cytolytic and cytoworks activity) or<br>primary NK cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|    |         |     |                   |                                       | disorders. Highly preferred            |
|----|---------|-----|-------------------|---------------------------------------|----------------------------------------|
|    |         |     |                   |                                       | indications also include cancers such  |
|    |         |     |                   |                                       | as, kidney, melanoma, prostate,        |
|    |         |     |                   |                                       | breast, lung, colon, pancreatic,       |
|    |         |     |                   |                                       | esophageal, stomach, brain, liver,     |
|    |         |     |                   |                                       | urinary cancer, lymphoma and           |
|    |         |     |                   |                                       | leukemias. Other preferred             |
|    |         |     |                   |                                       | indications include benign             |
|    |         |     |                   |                                       | dysproliferative disorders and pre-    |
|    |         |     |                   |                                       | neoplastic conditions, such as, for    |
|    |         |     |                   |                                       | example, hyperplasia, metaplasia,      |
|    |         |     |                   |                                       | and/or dysplasia. Other highly         |
|    |         |     |                   |                                       | preferred indications include,         |
|    |         |     |                   |                                       | pancytopenia, leukopenia, leukemias,   |
|    |         |     |                   |                                       | Hodgkin's disease, acute               |
|    |         |     |                   |                                       | lymphocytic anemia (ALL), arthritis,   |
|    |         |     |                   |                                       | asthma, AIDS, granulomatous            |
|    |         |     |                   |                                       | disease, inflammatory bowel disease,   |
|    |         |     |                   |                                       | sepsis, psoriasis, immune reactions to |
|    |         |     |                   |                                       | transplanted organs and tissues,       |
|    |         |     |                   |                                       | endocarditis, meningitis, Lyme         |
|    |         |     |                   |                                       | Disease, and allergies.                |
|    | HAIFL18 | 414 | Activation of     | Kinase assay. Kinase assays, for      | A highly preferred embodiment          |
| 10 |         |     | Adipocyte ERK     | example an Elk-1 kinase assay, for    | of the invention includes a method     |
|    |         |     | Signaling Pathway | ERK signal transduction that regulate | for stimulating adipocyte              |
|    |         |     |                   | cell proliferation or differentiation | proliferation. An alternative highly   |
|    |         |     |                   | are well known in the art and may be  | preferred embodiment of the            |
|    |         |     |                   | used or routinely modified to assess  | invention includes a method for        |
|    |         |     |                   | the ability of polypeptides of the    | inhibiting adipocyte proliferation.    |
|    |         |     |                   | invention (including antibodies and   | A highly preferred embodiment of       |
|    |         |     |                   | agonists or antagonists of the        | the invention includes a method for    |
|    |         |     |                   | invention) to promote or inhibit cell | stimulating adipocyte differentiation. |
|    |         |     |                   | proliferation, activation, and        | An alternative highly preferred        |
|    |         |     |                   | differentiation. Exemplary assays for | embodiment of the invention            |
|    |         |     |                   | ERK kinase activity that may be used  | includes a method for inhibiting       |
|    |         |     |                   | or routinely modified to test ERK     | adipocyte differentiation. A           |
|    |         |     |                   | kinase-induced activity of            | highly preferred embodiment of the     |

| polypeptides of the invention               | invention includes a method for                         | nethod for       |
|---------------------------------------------|---------------------------------------------------------|------------------|
| (including antibodies and agonists or       | ists or stimulating (e.g., increasing)                  | easing)          |
| antagonists of the invention) include       | _                                                       | An alternative   |
| the assays disclosed in Forrer et al.,      | t al., highly preferred embodiment of the               | odiment of the   |
| Biol Chem 379(8-9):1101-1110                | _                                                       | nethod for       |
| (1998); Le Marchand-Brustel Y, Exp          | , Exp   inhibiting the activation of (e.g.,             | on of (e.g.,     |
| Clin Endocrinol Diabetes                    | _                                                       | activating       |
| 107(2):126-132 (1999); Kyriakis JM,         | adipocytes.                                             | Highly preferred |
| Biochem Soc Symp 64:29-48 (1999);           | 1999);   indications include endocrine                  | docrine          |
| Chang and Karin, Nature                     | disorders (e.g., as described below                     | cribed below     |
| 410(6824):37-40 (2001); and Cobb            |                                                         | orders").        |
| MH, Prog Biophys Mol Biol 71(3-             |                                                         | cations also     |
| 4):479-500 (1999); the contents of          | of include neoplastic diseases (e.g.,                   | cases (e.g.,     |
| each of which are herein                    | lipomas, liposarcomas, and/or as                        | s, and/or as     |
| incorporated by reference in its            | _                                                       | Ŀ                |
| entirety. Mouse adipocyte cells that        | s that   "Hyperproliferative Disorders")                | Disorders").     |
| may be used according to these              |                                                         | include blood    |
| assays are publicly available (e.g.,        | g., disorders (e.g., hypertension,                      | tension,         |
| through the ATCC <sup>TM</sup> ). Exemplary |                                                         | re, blood vessel |
| mouse adipocyte cells that may be           | <ul> <li>be blockage, heart disease, stroke,</li> </ul> | se, stroke,      |
| used according to these assays              |                                                         | lescribed below  |
| include 3T3-L1 cells. 3T3-L1 is an          | _                                                       | rity",           |
| adherent mouse preadipocyte cell            | _                                                       | rders", and/or   |
| line that is a continuous substrain of      | _                                                       | ders"), immune   |
| 3T3 fibroblast cells developed              | ÷                                                       | cribed below     |
| through clonal isolation and undergo        | dergo   under "Immune Activity"), neural                | ity"), neural    |
| a pre-adipocyte to adipose-like             | disorders (e.g., as described below                     | cribed below     |
| conversion under appropriate                | under "Neural Activity and                              | y and            |
| differentiation conditions known in         | n in Neurological Diseases"), and                       | s"), and         |
| the art.                                    | infection (e.g., as described below                     | cribed below     |
|                                             | under "Infectious Disease"                              | ease").          |
|                                             | A highly preferred indication is                        | dication is      |
|                                             | diabetes mellitus.                                      | An additional    |
|                                             | highly preferred indication is a                        | ation is a       |
|                                             | complication associated with                            | ed with          |
|                                             | diabetes (e.g., diabetic retinopathy,                   | c retinopathy,   |
|                                             | diabetic nephropathy, kidney disease                    | kidney disease   |

|    |         |     |                    |                                      | Additional highly                       |
|----|---------|-----|--------------------|--------------------------------------|-----------------------------------------|
|    |         |     |                    |                                      | ndiontic                                |
|    |         |     |                    |                                      | the musculoskeletal systems             |
|    |         |     |                    |                                      | including myopathies, muscular          |
|    |         |     |                    |                                      | dystrophy, and/or as described          |
|    |         |     |                    |                                      | herein. Additional highly               |
|    |         |     |                    |                                      | preferred indications include,          |
|    |         |     |                    |                                      | hypertension, coronary artery           |
|    |         |     |                    |                                      | disease, dyslipidemia, gallstones,      |
|    |         |     |                    |                                      | ostcoarthritis, degenerative arthritis, |
|    |         |     |                    |                                      | eating disorders, fibrosis, cachexia,   |
|    |         |     |                    |                                      | and kidney diseases or disorders.       |
|    |         |     |                    |                                      | Preferred indications include           |
|    |         |     |                    |                                      | neoplasms and cancer, such as,          |
|    |         |     |                    |                                      | lymphoma, lcukemia and breast,          |
|    |         |     |                    |                                      | colon, and kidney cancer. Additional    |
|    |         |     |                    |                                      | preferred indications include           |
|    |         |     |                    |                                      | melanoma, prostate, lung,               |
|    |         |     |                    |                                      | pancreatic, esophageal, stomach,        |
|    |         |     |                    |                                      | brain, liver, and urinary cancer.       |
|    |         |     |                    |                                      | Highly preferred indications include    |
|    |         |     |                    |                                      | lipomas and liposarcomas. Other         |
|    |         |     |                    |                                      | preferred indications include benign    |
|    |         |     |                    |                                      | dysproliferative disorders and pre-     |
|    |         |     |                    |                                      | neoplastic conditions, such as, for     |
|    |         |     |                    |                                      | example, hyperplasia, metaplasia,       |
|    |         |     |                    |                                      | and/or dysplasia.                       |
|    | HAIFL18 | 414 | Production of      | IFNgamma FMAT. IFNg plays a          | A highly preferred embodiment           |
| 10 |         |     | IFNgamma using a T | central role in the immune system    | of the invention includes a method      |
|    |         |     | cells              | and is considered to be a            | for stimulating the production of       |
|    |         |     |                    | proinflammatory cytokine. IFNg       | IFNg. An alternative highly preferred   |
|    |         |     |                    | promotes TH1 and inhibits TH2        | embodiment of the invention             |
|    |         |     |                    | differentiation; promotes IgG2a and  | includes a method for inhibiting the    |
|    |         |     |                    | inhibits IgE secretion; induces      | production of IFNg. Highly              |
|    |         |     |                    | macrophage activation; and increases | preferred indications include blood     |
|    |         |     |                    | MHC expression. Assays for           | disorders (e.g., as described below     |
|    |         |     |                    | immunomodulatory proteins            | under "Immune Activity", "Blood-        |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | _                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| hyperplasia, metaplasia, and or<br>spesiblasia. Prefered infectations<br>include anemia, pancytopenia,<br>flettopenia, thembocytopenia,<br>Hodgkin's disease, acute<br>Hodgkin's disease, acute<br>mythoporitis entantia (ALL),<br>plastmacytomus, multiple myeloma,<br>plankti's kymposa, alimamour,<br>plankti's kymposa, alimamour,<br>gramulomnous disease, infarmanour,<br>neurophilia, poinsis, sappression<br>of immuse ventions to transplanted<br>organ and fistase, hemophilia,<br>hypercoagalation, disbetes mellins,<br>inpreroagalation, disbetes mellins,<br>hypercoagalation, disbetes mellins,<br>consensa, aktima and allergy. | A preferred tomboliment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly proferred enhodinents of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders, and excito below under framman Activity. "Blood-Related Disorders," and "C. "Cardiovascular diseases (e.g., rheumatol arthritis," Corbu's disease, multiple sclerosis immunodeficiencies (e.g. as described below). Immunodeficiencies (e.g. as in manifestics of the production present presents and mediated immune resones and mediated immune resones and mediated immune resones and mediated immune resones and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| incorporated by reference in its reference in its reference in its reference in the search of the property. Human Cells but may be used according to these assists may be solided using techniques disclosed herein or otherwise known in the art. Human Tedls are primary human lymphocytes that mature in human desprease at Tedl receptor and CD3, CD4, or CD8. These cells mediate humorel or cell-medical immunity and may be preadvived to enthance responsiveness to responsiveness to immunimomodulatory factors.                                                                                                                       | transaction through the Serum<br>Regesses Element (SRE) are well-<br>known in the art and may be used or<br>honown in the art and may be used or<br>honown in the art and may be used or<br>mainting or forphyperpides of the<br>ability of polyperpides of the<br>progression of programs of the<br>invention (robiding antibodies and<br>against or antegorises of the<br>invention) to regalate secun<br>invention) to regalate secun<br>invention) to regalate secun<br>to when the or program of<br>yours, have almost and modulate the<br>expression of genes involved in<br>copression of genes involved in<br>growth-related genes in many cell<br>of growth-related genes in many cell<br>through the SRE that<br>transactipion through the SRE and<br>transactipion through<br>the SRE activity of the polyperpides<br>transactipion through<br>transactivity of the polyperpides<br>transactivity of the polyperpide<br>transactivity of the polyperpide |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Archarion on the Archarion of the Archar                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 114                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HAIFLIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory        | disorders, and treating joint damage<br>in patients with rheumatoid arthritis.<br>An additional highly preferred<br>indication is sepsis. Highly | preferred indications include<br>morplastic diseases (e.g., leukemia,<br>lymphoma, andor as described<br>below under "Hyperproliferative<br>Disorders"). Additionally, highly         | preterred indications include ineoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant olioma), solid immors and mostate | breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinay cancer. Other preferred indications include benign dysampliferative disorders and medications include benign accorders and medications include benign and medications include benign and medications in the story of | uyspurucanve ukucus anu pre-<br>meoplastic conditions, such as, for<br>example, hyperplasia, metaplasia,<br>andor dysplasia. Preferred<br>indications include anemia,<br>pancytopenia, leukopenia,<br>pancytopenia, leukopenia, | disease, acute lymphocytic aremia (ALL), plasmacytomas, multiple myeloma, Burdut's lymphoma, arthritis, ALDS, granulomatous disease, inflarmatory bowel disease, metropenia, neurophilia, psoriasis, suppression of immune reactions to |
|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cullen and Malm, Methods in<br>Enzymol 216:362-368 (1992);<br>Henthom et al., Proc Natl Acad Sci<br>USA 85:6342-6346 (1988); Benson | et al., J Immunol 135(9):3862-3873<br>(1994), and Black et al., Virus Genes<br>12(2):105-117 (1997), the content of<br>each of which are herein  | incorporated by reference in its entirety. T cells that may be used according to these assays are publicity available (e.g., through the ATCC <sup>TM</sup> ). Exemplary T cells that | may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                         |
|                                                                                                                                     |                                                                                                                                                  |                                                                                                                                                                                       |                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                         |
|                                                                                                                                     |                                                                                                                                                  |                                                                                                                                                                                       |                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                         |
|                                                                                                                                     |                                                                                                                                                  |                                                                                                                                                                                       |                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                         |

| hemophilia, hyperoagulation,<br>diabetes mellins, endoardiis,<br>meningiis, Lyme Disease, cardiac<br>repertision injur, and saltma and<br>alleegy. An additional preferred<br>indication is infection (e.g., an<br>infections disease as described below<br>under "lifections Disease"). |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                          | Assays for measuing exclaim III.  are well-known in the art and may be added for underly modified to assess the shipty of polypergics of the mineralized or calcium. For example, the FITE was many to used to measure influx of calcium, extraocliniar column. Extraocliniar catacost and much ingher extraocliniar calcium. Extraocliniar catacost in each and an extraocliniar calcium. Extraocliniar calcium. Estraocliniar publivays and alterations in cell factors can ensure activation in that by polypergides of the invention including ambidous and alterations in Sant LS. et al. Endocrinology, 154(10):2560-5.  Endocrinology, 154(10):2560-5.  Endocrinology, 154(10):2560-5. |
|                                                                                                                                                                                                                                                                                          | Simulation of Calcium<br>Flux in pancreatic beta<br>cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                          | <u>v</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                          | HAJAND3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                          | Ξ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| (1992), and Amesa, Pre 1, Cell and Planchess, tules and impaired Calcium 1898 Nov-Dec; 10(89); 35441 wound healing, and infection (e.g., 10980), the contents of each of which is recurriery. Plancentic cells that may Diseases' section below, capocially be used coording to these assays and off the immary act and skin), applicablely available (e.g., through the brusted coording to these assays and off the immary residence and Duptyters? ATCP's and off may be brusted coording to the seases and everyone the cell time established from Syrian cells that may be used convoling to indications include viright loss or cell time established from Syrian changes it is a madherent polibelated and the cells of the | A seasy for the regulation of the companion of the compan |
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| (1992), and Masser, B.F. et al. (Cell Calcium) 1999 Non-Lpc-1(08.535.42).  Calcium) 1999 Non-Lpc-1(08.535.42).  Is herein incorpared by testine for the bit is nettered; Incorpared by the seasons and be used according to these assays and publicly available (e.g., Imongh the used according to these assays and the publicly available (e.g., Imongh the used according to these assays include HIIT15 Cells. The used according to these assays include HIIT15 Cells. The season's include HIIT15 Cells. The season's fine cell into established from Syrian cell line established from Syrian cell line established from Syrian Cells transformed with SW40. These cells transformed with Sw40. These cells captured by the search insulation of the samustantia and glucocardioid.  Exceptors. The cells are accele insulation of the samustantia and glucocardioid.  SW40. These cells are approxed by samusosatin or glucocardioids.  And Sw101. However, 1919 544-545, 1919 544-545, 1919. Local Ref. (1919. 544-544). To Ref. Local and Asherott. Brochem. 1, 219, 544-545. [19, 841, 4439, 4434, 1919.].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Regulation of Assays for the regulation of Assays for the regulation of transcription though the PEPCK the PEPCK promoter in promoter are well-known in the art hepatocytes and may be used or touringly modified to assess the ability of polypepides of the invention) to advise the PEPCK promoter in angulations for the invention) to activate the PEPCK promoter in a consequences. Exemplate liver glutonospecuesis. Exemplant activate the PEPCK promoter in a circum the PEPCK promoter in a consequence in the peper of the peper o |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HAIBR69 416                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| may be used or routinely modified to read to r |
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| Burgar et al., Gree 66:1-10 (1998);<br>Culler and Malm, Methods in<br>Enzymol 216:362-368 (1992);<br>Hembune al., Prov Natl Acad Sci<br>USA, 85:642-6446 (1988);<br>Lochbead et al., Disheres 496(1986-<br>903 (2000); and Yeagley et al., 1801<br>Chem 274(2);1781+17820 (2000).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| the contents of each of which is herein incorporated by reference in leven in morporated by reference in see arrivery. Heavenower cells that may be used according to these assays are publicly evaliable (e.g., through the ATCC VI) and/or may be voulunely generated. Exemplary lives to work the payamon cells that may be used according to these assays include according to the assays include with glucocorticoids, insulin, or cAMP derivatives.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|  |     | Additional highly preferred             |
|--|-----|-----------------------------------------|
|  |     | rectional inging presence               |
|  | T . | indications include glycogen storage    |
|  | 9   | disease (e.g., glycogenoses),           |
|  |     | hepatitis, gallstones, cirrhosis of the |
|  | _   | iver, degenerative or necrotic liver    |
|  |     | disease, alcoholic liver diseases,      |
|  | 4   | fibrosis, liver regeneration, metabolic |
|  |     | disease, dyslipidemia and cholesterol   |
|  | п   | metabolism, and hepatocarcinomas.       |
|  | -   | Highly preferred indications include    |
|  |     | blood disorders (e.g., as described     |
|  |     | below under "Immune Activity",          |
|  | •   | "Cardiovascular Disorders", and/or      |
|  | 3   | "Blood-Related Disorders"), immune      |
|  |     | disorders (e.g., as described below     |
|  | 1   | under "Immune Activity"), infection     |
|  |     | (e.g., an infectious disease and/or     |
|  |     | disorder as described below under       |
|  | •   | "Infectious Disease"), endocrine        |
|  |     | disorders (e.g., as described below     |
|  | 2   | under "Endocrine Disorders"), and       |
|  | 1   | neural disorders (e.g., as described    |
|  |     | below under "Neural Activity and        |
|  |     | Neurological Diseases").                |
|  | 7   | Additional preferred indications        |
|  | i   | include neoplastic diseases (e.g., as   |
|  | -0  | described below under                   |
|  | •   | "Hyperproliferative Disorders").        |
|  | I   | Preferred indications include           |
|  | 1   | neoplasms and cancers, such as,         |
|  |     | leukemia, lymphoma, prostate,           |
|  |     | breast, lung, colon, pancreatic,        |
|  | 9   | esophageal, stomach, brain, and         |
|  | _   | urinary cancer. A highly preferred      |
|  | ī   | indication is liver cancer. Other       |
|  | 14  | preferred indications include benign    |
|  | 9   | dysproliferative disorders and pre-     |

| neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dvsplasia. | A highly preferred embodiment of the investion includes a method for stimulating the production of GAC-SF. And attenuate highly preferred embodiment of the workston included for inhibiting the production of GAL-SF. And attenuate highly preferred indications include inflammation and additional highly preferred indications include inflammation of as described below under "Infectious Disease".  See J. Highly preferred indications include blood diseases (e.g., in INF infected pattents). In the production of the properties of the production of the processing of a particular of the processing of a particular of the processing of the procesi |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                         | GM-CSF FMAT. GN-CSF is propered policy and mercophage programors and enhances and mercophage monocycs and mercophage. The propered policy and propered policy and propered policy and monocycs, and important role in the differentiation in protection for the differentiation of Caledrice Colls and monocycs, and increases antigen presentation. GM-CSF page and monocycs, and increases antigen presentation. GM-CSF page and monocycle propered policy and monocycle and monocycle is considered to be a top for immunomodulatory proteins that promote the production of CRA-CSF page are well known in the art and may be mentionly to meditive and modified to assess the ability of polypopides of the immunomodulation and modulate the grounding and modulate the immunomodulation and modulate production of cytokines evaluate the production of cytokines immunomodulatory activition of polypopidiscs of the invention of programs of any evicinic of any evicinic of any evicinic of polyparics of the invention of production of cytokines.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                         | Production of GM-CSF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                         | 416                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                         | ПАЛВК69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                         | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Hodgkin's disease), and/or as<br>securited below under<br>"Hyperpoliterative Disorders").<br>Highly preferred indications include<br>to applaint and carriers, such as,<br>lettkerint, Iromphorn, melanoma, and<br>prostate, breast, lung, colon.                         | preferred infections include benign<br>yearberred infections include benign<br>yearberred infections include benign<br>when yearberred infections and pre-<br>neoplastic conditions, such as, for<br>example, hyperplasta, metaplasta,<br>mendo dyspassa, lirgiby preferred<br>indications include: suppression of<br>indications include: suppression of<br>indications include to transplant<br>everyery; and mobilizing<br>recovery; and mobilizing<br>recovery; and mobilizing.<br>Preferred indications include<br>boosting a T cell-mediated immune<br>response. The direction of the<br>suppressing a T cell-mediated<br>indications include anemia,<br>suppressing a T cell-mediated<br>indications include anemia,<br>thrombocytopenia, acute<br>throughous, acute indications include anemia,<br>thrombocytopenia, acute<br>thrombocytopenia, acute<br>preferred indications include anemia,<br>plasmacytomas, mittiple myeloma,<br>plasmacytomas, mittiple myeloma,<br>plasmacytomas, and medications, diabetes spellins,<br>byyeroxigi-indiano, diabetes mellins, | endocarditis, meningitis, Lyme<br>Disease, and allergy. |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| antagonists of the invention) include<br>the assays disclosed in Miraglia et<br>al., I Biomolecular Screening 4:193-<br>204 (1999), Rowland et al.,<br>"Lymphocytes: a practical approach"<br>(Chapter 6:138-160 (2000), and Ye et<br>al., I Leukoc Biol (58(2)):225-233, | therein incorporated by reference in its emircy. Natural silier cells that there is no properly a constitute of the season way be used according to these assays are publicly available (e.g., through the ATCC <sup>39</sup> ) or may be a constituted the companies of the control of otherwise from an inger breath or of otherwise from in the art. granular blieff (volt) cells are large protoxic activity but do brind antigen. Mk cells show authody-antigen by Red show authody-antigen by the companies on target cells, via MK fe receptors, leading to cell-mediated cytotoxicity, leading to cell-mediated cytotoxicity.                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                         |
|                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                         |
|                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                         |

| HAMFE15 | 417 | Regulation of         | Assays for the regulation of          | A highly preferred indication is       |
|---------|-----|-----------------------|---------------------------------------|----------------------------------------|
|         |     | transcription via     | transcription through the DMEF1       | diabetes mellitus. Additional highly   |
|         |     | DMEF1 response        | response element are well-known in    | preferred indications include          |
|         |     | element in adipocytes | the art and may be used or routinely  | complications associated with          |
|         |     | and pre-adipocytes    | modified to assess the ability of     | diabetes (e.g., diabetic retinopathy,  |
|         |     |                       | polypeptides of the invention         | diabetic nephropathy, kidney disease   |
|         |     |                       | (including antibodies and agonists or | (e.g., renal failure, nephropathy      |
|         |     |                       | antagonists of the invention) to      | and/or other diseases and disorders as |
|         |     |                       | activate the DMEF1 response           | described in the "Renal Disorders"     |
|         |     |                       | element in a reporter construct (such | section below), diabetic neuropathy,   |
|         |     |                       | as that containing the GLUT4          | nerve disease and nerve damage         |
|         |     |                       | promoter) and to regulate insulin     | (e.g., due to diabetic neuropathy),    |
|         |     |                       | production. The DMEF1 response        | blood vessel blockage, heart disease,  |
|         |     |                       | element is present in the GLUT4       | stroke, impotence (e.g., due to        |
|         |     |                       | promoter and binds to MEF2            | diabetic neuropathy or blood vessel    |
|         |     |                       | transcription factor and another      | blockage), seizures, mental            |
|         |     |                       | transcription factor that is required | confusion, drowsiness, nonketotic      |
|         |     |                       | for insulin regulation of Glut4       | hyperglycemic-hyperosmolar coma,       |
|         |     |                       | expression in skeletal muscle.        | cardiovascular disease (e.g., heart    |
|         |     |                       | GLUT4 is the primary insulin-         | disease, atherosclerosis,              |
|         |     |                       | responsive glucose transporter in fat | microvascular disease, hypertension,   |
|         |     |                       | and muscle tissue. Exemplary assays   | stroke, and other diseases and         |
|         |     |                       | that may be used or routinely         | disorders as described in the          |
|         |     |                       | modified to test for DMEF1 response   | "Cardiovascular Disorders" section     |
|         |     |                       | element activity (in adipocytes and   | below), dyslipidemia, endocrine        |
|         |     |                       | pre-adipocytes) by polypeptides of    | disorders (as described in the         |
|         |     |                       | the invention (including antibodies   | "Endocrine Disorders" section          |
|         |     |                       | and agonists or antagonists of the    | below), neuropathy, vision             |
|         |     |                       | invention) include assays disclosed   | impairment (e.g., diabetic retinopathy |
|         |     |                       | inThai, M.V., et al., J Biol Chem,    | and blindness), ulcers and impaired    |
|         |     |                       | 273(23):14285-92 (1998); Mora, S.,    | wound healing, and infection (e.g.,    |
|         |     |                       | et al., J Biol Chem, 275(21):16323-8  | infectious diseases and disorders as   |
|         |     |                       | (2000); Liu, M.L., et al., J Biol     | described in the "Infectious           |
|         |     |                       | Chem, 269(45):28514-21 (1994);        | Discases" section below, especially    |
|         |     |                       | "Identification of a 30-base pair     | of the urinary tract and skin). An     |
|         |     |                       | regulatory element and novel DNA      | additional highly preferred indication |
|         |     |                       | binding protein that regulates the    | is obesity and/or complications        |

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| 3 - 0 - 1 - 1                                | 7 - 7                                  |
|----------------------------------------------|----------------------------------------|
| Identity can cause an initial of             | suove, impotence (e.g., due to         |
| calcium, leading to activation of            | diabetic neuropathy or blood vessel    |
| calcium responsive signaling                 | blockage), seizures, mental            |
| pathways and alterations in cell             | confusion, drowsiness, nonketotic      |
| functions. Exemplary assays that             | hyperglycemic-hyperosmolar coma,       |
| may be used or routinely modified to         | cardiovascular disease (e.g., heart    |
| measure calcium flux by                      | disease, atherosclerosis,              |
| polypeptides of the invention                | microvascular disease, hypertension,   |
| (including antibodies and agonists or        | stroke, and other diseases and         |
| antagonists of the invention) include        | disorders as described in the          |
| assays disclosed in: Satin LS, et al.,       | "Cardiovascular Disorders" section     |
| Endocrinology, 136(10):4589-601              | below), dyslipidemia, endocrine        |
| (1995);Mogami H, et al.,                     | disorders (as described in the         |
| Endocrinology, 136(7):2960-6                 | "Endocrine Disorders" section          |
| (1995); Richardson SB, et al.,               | below), neuropathy, vision             |
| Biochem J, 288 (Pt 3):847-51                 | impairment (e.g., diabetic retinopathy |
| (1992); and, Meats, JE, et al., Cell         | and blindness), ulcers and impaired    |
| Calcium 1989 Nov-Dec;10(8):535-41            | wound healing, and infection (e.g.,    |
| (1989), the contents of each of which        | infectious diseases and disorders as   |
| is herein incorporated by reference in       | described in the "Infectious           |
| its entirety. Pancreatic cells that may      | Diseases" section below, especially    |
| be used according to these assays are        | of the urinary tract and skin), carpal |
| publicly available (e.g., through the        | ome a                                  |
| ATCC <sup>TM</sup> ) and/or may be routinely | contracture). An additional            |
| generated. Exemplary pancreatic              | highly preferred indication is obesity |
| cells that may be used according to          | and/or complications associated with   |
| these assays include HTT15 Cells.            | obesity. Additional highly preferred   |
| HITT15 are an adherent epithelial            | indications include weight loss or     |
| cell line established from Syrian            | alternatively, weight gain.            |
| hamster islet cells transformed with         | Aditional highly preferred             |
| SV40. These cells express glucagon,          | indications are complications          |
| somatostatin, and glucocorticoid             | associated with insulin resistance.    |
| receptors. The cells secrete insulin,        |                                        |
| which is stimulated by glucose and           |                                        |
| glucagon and suppressed by                   |                                        |
| somatostatin or glucocorticoids.             |                                        |
| ATTC# CRL-1777 Refs: Lord and                |                                        |

|                                                                                                           | A highly preferred embodiment of the invention includes a method for simulating adjrocyte a method for simulating adjrocyte anethod for remember of the simulating adjrocyte method for inhibiting adjrocyte positicention. In the invention includes a method for inhibiting adjrocyte positicention. In the invention includes a method for inhibiting adjrocyte positicention. An alternative highly preferred embodiment of the invention includes a method for inhibiting another of the invention includes a method for includes an anethod for inhibiting another of the invention includes a method for simulating (e.g., increasing) increasing an embod for simulating (e.g., increasing) increasing an embod for inhibiting and or includes an embod for inhibiting the activesion of (e.g., decreasing) and or inectivating effects of the inhibiting the activesion of (e.g., decreasing) and or inectivating effects of the inhibiting the active of the formal includes an embod for inhibiting the active of the Control English preferred indications include endocrine discusses (e.g., light) preferred indications include endocrine described below under "Endocrine Disorders"). Preferred indications include bood described below under "Endocrine Disorders"). Preferred indications include bood described below under securitive beart failure by host events.             |
|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ashcroft. Biochem. J. 219: 547-551;<br>Santerre et al. Proc. Natl. Acad. Sci.<br>USA 78: 4339-4343, 1981. | times neary, Kinesa ensury, for example an IELL kinnes assay, for IERK agnal transduction that regulate cell positive and in IELL kinnes assay, for the standard of rounding by modified to assess the ability of polypepidase of the invention (including anthodies and agonisis or anagonisis of the anagonisis of anagonisis of anagonisis of anagonisis of the invention (including anthodies and agonisis or not minely modified to test IERK kinnes extivity that may be used. IRK kinnes extivity that may be used the invention including anthodies and agonist or orthinely modified to test IERK kinnes extivity that may be used (including anthodies and agonist or the savys disclosed in Forcer et al. (1998); Le Marchard-Brossel Y, Exp. Clin Endocrion Dubeiess. Clin Endocrion Dubeiess (1998); Le Marchard-Brossel Y, Exp. Clin Endocrion Dubeiess (1998); Le Marchard-Brossel Y, Exp. Clin Endocrion Dubeiess (1998); Le Amerhard-Brossel Y, Exp. Clin Endocrion Dubeiess (1998); Le Amerhard-Brossel V, Exp. Clin Endocrion Dubeiess and the Regulation of the standard of vibried are bettern in encopromed by reference in its entirety. Mouse advocyted and ecoeding to these analysis of each further may be used according to these analysis of each further may be used according to these |
|                                                                                                           | Activation of Activation of Adjacosyle Algorithms Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                           | 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                           | HAPPS803                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                           | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| blockage, heart disease, stroke,  | impotence and/or as described below | "Condigues Discussion," and/or | _                            | _                                     | under "Immune Activity") neurol      | _                               | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | discase, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine |
|-----------------------------------|-------------------------------------|--------------------------------|------------------------------|---------------------------------------|--------------------------------------|---------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|
| mouse adipocyte cells that may be | used according to these assays      | adhount mono amodiacorto cell  | amerem mouse preampocyte cen | inc that is a continuous substrain of | through closed icolation and undergo | a pre-adipocyte to adipose-like | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |
|                                   |                                     |                                |                              |                                       |                                      |                                 |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |
|                                   |                                     |                                |                              |                                       |                                      |                                 |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    | _                               |

|  | disorders (as described in the          | ed in the          |
|--|-----------------------------------------|--------------------|
|  | "Endocrine Disorders" section           | s" section         |
|  | inmairment (e.g., diabetic retinonathy  | thetic retinopathy |
|  | and blindness), ulcers and impaired     | s and impaired     |
|  | wound healing, infection (e.g.,         | zion (e.g.,        |
|  | infectious diseases and disorders as    | nd disorders as    |
|  | described in the "Infectious            | ections            |
|  | Diseases" section below (particularly   | low (particularly  |
|  | of the urinary tract and skin).         | nd skin). An       |
|  | additional highly preferred indication  | ferred indication  |
|  | is obesity and/or complications         | aplications        |
|  | associated with obesity. Additional     | ity. Additional    |
|  | highly preferred indications include    | cations include    |
|  | weight loss or alternatively, weight    | atively, weight    |
|  | gain. Additional highly                 | al highly          |
|  | preferred indications are               | are                |
|  | complications associated with insulin   | ated with insulin  |
|  | resistance. Ad                          | Additional highly  |
|  | preferred indications are disorders of  | are disorders of   |
|  | the musculoskeletal systems             | systems            |
|  | including myopathies, muscular          | s, muscular        |
|  | dystrophy, and/or as described          | described          |
|  | herein. Additional highly               | al highly          |
|  | preferred indications include,          | include,           |
|  | hypertension, coronary artery           | ıry artery         |
|  | disease, dyslipidemia, gallstones,      | a, gallstones,     |
|  | osteoarthritis, degenerative arthritis, | erative arthritis, |
|  | eating disorders, fibrosis, cachexia,   | osis, cachexia,    |
|  | and kidney diseases or disorders.       | or disorders.      |
|  | Preferred indications include           | s include          |
|  | neoplasms and cancer, such as,          | er, such as,       |
|  | lymphoma, leukemia and breast,          | and breast,        |
|  | colon, and kidney cancer. Additional    | ncer. Additional   |
|  | preferred indications include           | include :          |
|  | melanoma, prostate, lung,               | hung,              |
|  | pancreatic, esophageal, stomach         | al, stomach,       |

| heain, liver, and urinary cancer. Highly poefected indications include. Highly poefected indications include being preferred indications include being symptoliteative disorders and preparative conditions, such as, for example, typispilissis, metaplissis, and/or dyspissis, and/or dyspissis, and/or dyspissis. | A highly preferred cambdinear of the invention includes a method regular for stimulating disposers are stimulated for stimulating disposers are seen predicted and an experience demonstrate highly preferred cambdinears of the invention includes a method for include and the invention includes a method for include and the invention includes a method for include as method for the invention includes a method for include as method for include a method for including the dispose of includes a method for including the dispose of includes a method for includes a method for including the dispose of includes a method for including the dispose of includes a method for including the dispose of includes a method for including the disposers of the including disposers of the including disposers of |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                      | Kinnea seasy, Citations assays, for comple at IRI-I kinnea seasy, for the stage of  |
|                                                                                                                                                                                                                                                                                                                      | 420 Activation of Adjopaya BRK Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                      | 16 HAPNY94                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

|   |                                  | <u></u>                              | poold                               |                                      | d vessel                               | 9,                                | d below                             |                                    | nd/or                              | mmnne                                 | elow                                | ural                                 | elow                                |                              |                                     | elow                               |                              | is                               | An additional      | es                               |                              | athy,                                 | disease                              | λíc                               | orders as                              | ders"                              | pathy,                               | 96                             | hy),                               | lisease,                              | •                               | vessel                              |                             | totic                             | coma,                            | eart                                |                         |
|---|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|------------------------------------|------------------------------|----------------------------------|--------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|-------------------------|
|   | der                              | : Disorder:                          | is include                          | ertension,                           | lure, bloo                             | ease, strok                       | s describe                          | tivity",                           | sorders", a                        | sorders"),                            | escribed b                          | tivity"), no                         | escribed b                          | vity and                     | ses"), and                          | escribed b                         | isease").                    | indication                       | An ad              | lication is                      | iated with                   | etic retinor                          | ny, kidney                           | nephropat                         | ss and disc                            | enal Disor                         | betic neuro                          | erve dame                      | c neuropai                         | ige, heart o                          | e.g., due to                    | or blood                            | , mental                    | ess, nonke                        | erosmolar                        | ase (e.g., k                        | 0100                    |
|   | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | clockage, heart disease, stroke,  | impotence and/or as described below | inder "Immune Activity"            | 'Cardiovascular Disorders', and/or | 'Blood-Related Disorders"), immune    | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | inder "Neural Activity and   | Neurological Diseases"), and        | nfection (e.g., as described below | inder "Infectious Disease"). | A highly preferred indication is | liabetes mellitus. | nighly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy) | clood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | dispass atherocolorosis |
|   | describe                         | "Hyperp                              | Preferre                            | disorders                            | congesti                               | blockage                          | impotenc                            | under "I                           | "Cardio                            | "Blood-l                              | disorders                           | under "In                            | disorders                           | under "N                     | Neurolog                            | infection                          | under "In                    | A highly                         | diabetes           | highly pa                        | complica                     | diabetes                              | diabetic                             | (e.g., ren                        | and/or of                              | describe                           | section b                            | nerve dis                      | (e.g., due                         | blood ve                              | stroke, ir                      | diabetic                            | blockage                    | confusio                          | hypergly                         | cardiova                            | dicease                 |
|   | its                              | alls that                            | sc                                  | (e.g.,                               | plary                                  | ay be                             | 8/                                  | 1 is an                            | cell :                             | train of                              | p                                   | undergo                              | e                                   |                              | own in                              |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   | ference in                       | lipocyte ca                          | ding to the                         | available                            | TM). Exer                              | ells that m                       | hese assay                          | ls. 3T3-L                          | eadipocyte                         | sqns snon                             | s develope                          | ation and                            | adipose-li                          | ppropriate                   | ditions kn                          |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | ine that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   | incorpor                         | entirety.                            | may be t                            | assays an                            | through                                | mouse a                           | used acc                            | include                            | adherent                           | line that                             | 3T3 fibr                            | through                              | a pre-adi                           | conversi                     | different                           | the art.                           |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
| ŀ |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   | _                                |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|   |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                    |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |

| _ |  | microvascular disease hynertension      |
|---|--|-----------------------------------------|
|   |  | studio and other discous and            |
|   |  | stroke, and other diseases and          |
| _ |  | disorders as described in the           |
|   |  | "Cardiovascular Disorders" section      |
| _ |  | below), dyslipidemia, endocrine         |
| _ |  | disorders (as described in the          |
|   |  | "Endocrine Disorders" section           |
|   |  | below), neuropathy, vision              |
|   |  | impairment (e.g., diabetic retinopathy  |
|   |  | and blindness), ulcers and impaired     |
|   |  | wound healing, infection (e.g.,         |
|   |  | infectious diseases and disorders as    |
|   |  | described in the "Infectious            |
|   |  | Diseases" section below (particularly   |
|   |  | of the urinary tract and skin). An      |
|   |  | additional highly preferred indication  |
| _ |  | is obesity and/or complications         |
| _ |  | associated with obesity. Additional     |
|   |  | highly preferred indications include    |
|   |  | weight loss or alternatively, weight    |
|   |  | gain. Additional highly                 |
| _ |  | preferred indications are               |
|   |  | complications associated with insulin   |
|   |  | resistance. Additional highly           |
|   |  | preferred indications are disorders of  |
| _ |  | the musculoskeletal systems             |
|   |  | including myopathies, muscular          |
| _ |  | dystrophy, and/or as described          |
| _ |  | herein. Additional highly               |
|   |  | preferred indications include,          |
|   |  | hypertension, coronary artery           |
| _ |  | disease, dyslipidemia, gallstones,      |
|   |  | osteoarthritis, degenerative arthritis, |
|   |  | eating disorders, fibrosis, cachexia,   |
|   |  | and kidney diseases or disorders.       |
|   |  | Preferred indications include           |
|   |  | neoplasms and cancer, such as,          |

| the prophoran, leuternia and broast, colon, and kithey concer. Additional preferred indications include and indications include mental mental properties, long punceracie, esophageal, someth, leuter, and trainary concer. Highly preferred indications include preferred indications include brange preferred indications include brange preferred indications include brange preferred indications and pre-no-plastic conditions, such as, for example, hyporplisai, metalpissia, and/or dysplastic. | thighty preferred indication is diabetes mellitus. An additional inheby preferred indication is all adhity preferred indication is all adhity preferred indication is all complication associated with diabetes (e.g., diabetic extempathy, kidned clienses (e.g., renal faither, nephropathy additional factor of the fastes and disorders as described in the "Reant Disorders" according below, placetic memopathy, nerve disasses and nerve diamage (e.g., due to diabetic neuropathy, thood vessel bockeage, heart disease, and the state of the property of the processes, mernal blockeage, sextraces, mernal blockeage, sextraces, mernal blockeage, sextraces, mernal blockeage, sextraces, mernal disease, althorogenesis, and disease, althorogenesis, and disease, althorogenesis.                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | and proliferation of cells in vitro and Proliferation of cells in vitro and well-known in the art and may be used or routinedly modified to assess the ability of polypeptides of the mention (inclining ambidoites and agonists or amagonists of the routino) to rolliferation of pancreate bed cells in remembod to regulate viability and polylication of pancreate bed cells luminescent cell viability assay in casame to example, the Cell Tuter-Glo luminescent cell viability assay in colline besed on quantitation of measures the number of viability assay in colline besed on quantitation of presence of metabolically active cells. Exemplary assays that may be presence of metabolically active cells. Exemplary assays that may be oblypeptides of the invention of viability and inferioration include and antagonists of the invention include and and in Archaevined 18.4. Vi 12.4.8. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | and publication of paracretic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 421                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | НАРОМ49                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|    |         |     |                                                 | Find Double House, 13, 144, 144, 144, 144, 144, 144, 144,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | disorders (ed searched in the disorders (ed searched in the disorders (ed searched in the helm). That docume Disorders' section below), neuropathy, vision impairment (e.g., diabetic retimopathy and bluthness), those and disorders and singuistic and searched in the "Infections searched in the "Infections as disorsed and searched in the "Infection as descarbed in the "Infection searched" and seth, certain of the urimary tract and skin), certain sourceaure). An additional highly preferred indication in debeying and, additional highly preferred indications and alternatively, weight gain, Additional alternatively, weight gain, Additional alternatively, weight gain, Additional resistance. |
|----|---------|-----|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 81 | HAPUC89 | 422 | Activation of Adjusting BIK Signaling Petitiway | the mean season, former access, for example on III-L fairnes access, for TRK Agend transduction that regulate cell proliferation or differentiation are well known in the art out may be act or rountinely nodified to assess the ability of polypeptides of the transmission of the properties of the remained to the properties of the agents of the profit of | A highly preferred embediment of the Prevention includes a method for attimitating adhocyte we already to highly preferred on An already to highly preferred embediment of the inthibiting adjacoty proliferation. A thaily preferred embediment of the inthibiting adjacoty proliferation the invention includes a method for inthibiting adjacoty edifferentiation. An alternative highly preferred an additional and a method for the invention includes a method for inhibiting includes a method for inhibiting and approve afferentiation. A language of the method for inhibiting and a proposed the intentiation. A language and a preferred embediment of the includes a method for inhibiting                                                                                                                                     |

| nolvneptides of the invention               | invention includes a method for        |
|---------------------------------------------|----------------------------------------|
| (including antibodies and agonists or       | stimulating (e.g., increasing)         |
| antagonists of the invention) include       | adipocyte activation. An alternative   |
| the assays disclosed in Forrer et al.,      | highly preferred embodiment of the     |
| Biol Chem 379(8-9):1101-1110                | invention includes a method for        |
| (1998); Le Marchand-Brustel Y, Exp          | inhibiting the activation of (e.g.,    |
| Clin Endocrinol Diabetes                    | decreasing) and/or inactivating        |
| 107(2):126-132 (1999); Kyriakis JM,         | adipocytes. Highly preferred           |
| Biochem Soc Symp 64:29-48 (1999);           | indications include endocrine          |
| Chang and Karin, Nature                     | disorders (e.g., as described below    |
| 410(6824):37-40 (2001); and Cobb            | under "Endocrine Disorders").          |
| MH, Prog Biophys Mol Biol 71(3-             | Highly preferred indications also      |
| 4):479-500 (1999); the contents of          | include neoplastic diseases (e.g.,     |
| each of which are herein                    | lipomas, liposarcomas, and/or as       |
| incorporated by reference in its            | described below under                  |
| entirety. Mouse adipocyte cells that        | "Hyperproliferative Disorders").       |
| may be used according to these              | Preferred indications include blood    |
| assays are publicly available (e.g.,        | disorders (e.g., hypertension,         |
| through the ATCC <sup>TM</sup> ). Exemplary | congestive heart failure, blood vessel |
| mouse adipocyte cells that may be           | blockage, heart disease, stroke,       |
| used according to these assays              | impotence and/or as described below    |
| include 3T3-L1 cells. 3T3-L1 is an          | under "Immune Activity",               |
| adherent mouse preadipocyte cell            | "Cardiovascular Disorders", and/or     |
| line that is a continuous substrain of      | "Blood-Related Disorders"), immune     |
| 3T3 fibroblast cells developed              | disorders (e.g., as described below    |
| through clonal isolation and undergo        | under "Immune Activity"), neural       |
| a pre-adipocyte to adipose-like             | disorders (e.g., as described below    |
| conversion under appropriate                | under "Neural Activity and             |
| differentiation conditions known in         | Neurological Diseases"), and           |
| the art.                                    | infection (e.g., as described below    |
|                                             | under "Infectious Disease").           |
|                                             | A highly preferred indication is       |
|                                             | diabetes mellitus. An additional       |
|                                             | highly preferred indication is a       |
|                                             | complication associated with           |
|                                             | diabetes (e.g., diabetic retinopathy,  |
|                                             | diabetic nephropathy, kidney disease   |

| (e.g., renal failure, nephropathy and/or other diseases and disorders as |
|--------------------------------------------------------------------------|
| described in the "Renal Disorders"                                       |
| section below), diabetic neuropathy,                                     |
| nerve disease and nerve damage (e.g., due to diabetic neuropathy),       |
| blood vessel blockage, heart disease,                                    |
| stroke, impotence (e.g., due to                                          |
| diabetic neuropathy or blood vessel                                      |
| blockage), seizures, mental                                              |
| confusion, drowsiness, nonketotic                                        |
| hyperglycemic-hyperosmolar coma,                                         |
| cardiovascular disease (e.g., heart                                      |
| disease, atherosclerosis,                                                |
| microvascular disease, hypertension,                                     |
| stroke, and other diseases and                                           |
| disorders as described in the                                            |
| "Cardiovascular Disorders" section                                       |
| below), dyslipidemia, endocrine                                          |
| disorders (as described in the                                           |
| "Endocrine Disorders" section                                            |
| below), neuropathy, vision                                               |
| impairment (e.g., diabetic retinopathy                                   |
| and blindness), ulcers and impaired                                      |
| wound healing, infection (e.g.,                                          |
| infectious diseases and disorders as                                     |
| described in the "Infectious                                             |
| Diseases" section below (particularly                                    |
| of the urinary tract and skin). An                                       |
| additional highly preferred indication                                   |
| is obesity and/or complications                                          |
| associated with obesity. Additional                                      |
| highly preferred indications include                                     |
| weight loss or alternatively, weight                                     |
| gain. Additional highly                                                  |
| preferred indications are                                                |
| complications associated with insulin                                    |

|    |         |     |                       |                                       | resistance. Additional highly           |
|----|---------|-----|-----------------------|---------------------------------------|-----------------------------------------|
|    |         |     |                       |                                       | preferred indications are disorders of  |
|    |         |     |                       |                                       | the musculoskeletal systems             |
|    |         |     |                       |                                       | including myopathies, muscular          |
|    |         |     |                       |                                       | dystrophy, and/or as described          |
|    |         |     |                       |                                       | herein. Additional highly               |
|    |         |     |                       |                                       | preferred indications include,          |
|    |         |     |                       |                                       | hypertension, coronary artery           |
|    |         |     |                       |                                       | discase, dyslipidemia, gallstones,      |
|    |         |     |                       |                                       | ostcoarthritis, degenerative arthritis, |
|    |         |     |                       |                                       | eating disorders, fibrosis, cachexia,   |
|    |         |     |                       |                                       | and kidney diseases or disorders.       |
|    |         |     |                       |                                       | Preferred indications include           |
|    |         |     |                       |                                       | neoplasms and cancer, such as,          |
|    |         |     |                       |                                       | lymphoma, leukemia and breast,          |
|    |         |     |                       |                                       | colon, and kidney cancer. Additional    |
|    |         |     |                       |                                       | preferred indications include           |
|    |         |     |                       |                                       | melanoma, prostate, lung,               |
|    |         |     |                       |                                       | pancreatic, esophageal, stomach,        |
|    |         |     |                       |                                       | brain, liver, and urinary cancer.       |
|    |         |     |                       |                                       | Highly preferred indications include    |
|    |         |     |                       |                                       | lipomas and liposarcomas. Other         |
|    |         |     |                       |                                       | preferred indications include benign    |
|    |         |     |                       |                                       | dysproliferative disorders and pre-     |
|    |         |     |                       |                                       | neoplastic conditions, such as, for     |
|    |         |     |                       |                                       | example, hyperplasia, metaplasia,       |
|    |         |     |                       |                                       | and/or dysplasia.                       |
|    | HAPUC89 | 422 | Activation of         | This reporter assay measures          | Highly preferred indications include    |
| 81 |         |     | transcription through | activation of the NFAT signaling      | allergy, asthma, and rhinitis.          |
|    |         |     | NFAT response         | pathway in HMC-1 human mast cell      | Additional preferred indications        |
|    |         |     | element in immune     | line. Activation of NFAT in mast      | include infection (e.g., an infectious  |
|    |         |     | cells (such as mast   | cells has been linked to cytokine and | discase as described below under        |
|    |         |     | cells).               | chemokine production. Assays for      | "Infectious Disease"), and              |
|    |         |     |                       | the activation of transcription       | inflammation and inflammatory           |
|    |         |     |                       | through the Nuclear Factor of         | disorders. Preferred indications also   |
|    |         |     |                       | Activated T cells (NFAT) response     | include blood disorders (e.g., as       |
|    |         |     |                       | element are well-known in the art     | described below under "Immune           |

| and may be used or routinely monthing by more first on season the ability of polyprophics of the invention (including antickies and its agonis or antique) and the invention) to regulate WPK The meast-prior in framest-prior in functions. Exemplar Season's and modulate expression of genes invention of the monthing the WEAT response element that may be used to response element that may be used to response element that may be used to response element that may be used to response element that more than the control of polyperidis of the invention) include assers of element of the invention of leading antipolicity of the invention of leading assers of element of 10 1999; Culten and Malla Methods in inspanding and the control of the leading antipolicity of the leading and the leading of the leading that has been easily as my publishy available (e.g., through the used according to the seasy as are publishy available (e.g., through the used according to the seasy as are publishy available (e.g., through the used according to the seasy as are publishy available (e.g., through the used according to the seasy are publishy available (e.g., through the used according to the seasy are publishy available (e.g., through the used according to the seasy are publishy availabl | ľ                            | f Disorders", and/or "Cardiovascular | Disorders"). Preferred indications | ists or   include autoimmune diseases (e.g., | _                                | ctors erythematosis, multiple sclerosis | nes and/or as described below) and |                             | _                           |                               | used or diseases (e.g., leukemia, lymphoma, |                                | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary | _                              | clude   below under "Hyperproliferative | ., Disorders"). Other preferred |                               | dysproliferative disorders and pre- | et al., neoplastic conditions, such as, for | J.                           | -                               | 1-1236 indications include anemia, | pancytopenia, leukopenia,     | _                         | _                           | _                          | _                            |                               |                          | bowel disease, sepsis, neutropenia, | e used   neutrophilia, psoriasis, suppression | ublicly of immune reactions to transplanted | organs and tissues, hemophilia, | mast hypercoagulation, diabetes mellitus, | g to endocarditis, meningitis, and Lyme |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------|------------------------------------|----------------------------------------------|----------------------------------|-----------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|---------------------------------------------|--------------------------------|--------------------------------|------------------------------------|--------------------------------|-----------------------------------------|---------------------------------|-------------------------------|-------------------------------------|---------------------------------------------|------------------------------|---------------------------------|------------------------------------|-------------------------------|---------------------------|-----------------------------|----------------------------|------------------------------|-------------------------------|--------------------------|-------------------------------------|-----------------------------------------------|---------------------------------------------|---------------------------------|-------------------------------------------|-----------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and may be used or routinely | modified to assess the ability of    | polypeptides of the invention      | (including antibodies and agor               | antagonists of the invention) to | regulate NFAT transcription fa          | and modulate expression of ge      | involved in immunomodulator | functions, Exemplary assays | transcription through the NFA | response element that may be                | routinely modified to test NFA | response element activity of   | polypeptides of the invention      | (including antibodies and agor | antagonists of the invention) ii        | assays disclosed in Berger et a | Gene 66:1-10 (1998); Cullen a | Malm, Methods in Enzymol            | 216:362-368 (1992); Henthorn                | Proc Natl Acad Sci USA 85:6: | 6346 (1988); De Boer et al., Ir | Biochem Cell Biol 31(10):122       | (1999); Ali et al., J Immunol | 165(12):7215-7223 (2000); | Hutchinson and McCloskey, J | Chem 270(27):16333-16338 ( | and Turner et al., J Exp Med | 188:527-537 (1998), the conte | each of which are herein | incorporated by reference in it     | entirety. Mast cells that may b               | according to these assays are p             | available (e.g., through the    | ATCC <sup>TM</sup> ). Exemplary human     | cells that may be used accordi          |

|                                                                                                                                                                                       | Highly preferred indications include crudo-rine diseasers in include crudo-rine diseasers (e.g., us described betwo made "Parlocrime mususkichetal system." Perford indicatorius include reported indicatorius include nooplastic diseases (e.g., us described nooplastic diseases (e.g., us described below under "Immune Activity", "Cardiovascallar Activity", "Cardiovascallar manue for "Immune Activity", "Cardiovascallar monther "Immune Activity", "Cardiovascallar below under "Immune Activity", "Immune disorders (e.g., us described below under "Includio as described below under "Includio State of the Activity" and when disorders (e.g., us described below under "Includio State of State o |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells. | way Kinness ussuys, for The Likiness ussuys, for The Likiness ussuys, for The Likiness of the Characterion in the regulate ratios or office-randarion owns in the art and may be made you follow the season of propagatides of the including antibodics and unatagonists of the or pornounce or minhi cell on personness or the exemplay assays for exercivity into may be used you desired to the season of the invention include cost for the invention include and antibodics and agonisis or or of the invention include disclosed and agonisis or or of the invention include disclosed and approach a fraging and possible and agonisis or or of the invention include disclosed in Forner et al., 273(4.9.9.); II to 1110 Marchard-Phasel Y. Exp. 7.122 (1999); Karin, Naure Cobb Bloophys, Mod Biod 71(3.4.0.001); and Cobb Bloophys Mod Biod 71(4.4.0.001); and cobb Bloophys Roberts of Hat may bear in inspections of interpretation in the part and by reference in its part and myoblast cells that may                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                       | Activation of Steletal Muscle Cell FIRK Signalling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                       | 422                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                       | HAPUC89                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                       | 89                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|   |         |     |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | myopathies, muscular dystrophy, and ora s destribed bretin. Additional lightly preferred important importa |
|---|---------|-----|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6 | HATBR65 | 423 | Production of IL-6 | IL-6 FMAT. IL-6 is produced by T<br>cells and has strong effects on B<br>cells. IL-6 principacies in IL-4<br>induced leg production and increases<br>legs production (e.g. phys a role in<br>muscust immunity). IL-6 induces<br>expression of IL-6 has been inhed to<br>covorics T cells. Dergalandel<br>expression of IL-6 has been inhed to<br>myelomas, and oltonio<br>hyperpolificative diseases. Assays<br>for immunomaliatory and differentiation factor proteins<br>hyperpolificative diseases. Assays<br>differentiation factor proteins<br>showted by a ladge winey of cells<br>where the expression level is strongly. | meneplasis, and/or dysplusia.  Halpin preterred ambuliment of the invention includes a method for increasing) Life production. An alternative lightly preduction to a later of the invention includes a method for invention includes a simulation or enhancement of innewal immunity. Highly preferred infections anchold below under "Immune Activity" is also distorders (a and or standors and or standors and includes and sinceders (a. as described below under "Immune Activity").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| regulated by cytokines, growin         | infection (e.g., as described below    |
|----------------------------------------|----------------------------------------|
| factors, and hormones are well         | under "Infectious Disease"). Highly    |
| known in the art and may be used or    | preferred indications include          |
| routinely modified to assess the       | autoimmune diseases (e.g.,             |
| ability of polypeptides of the         | rheumatoid arthritis, systemic lupus   |
| invention (including antibodies and    | erythematosis, multiple sclerosis      |
| agonists or antagonists of the         | and/or as described below) and         |
| invention) to mediate                  | immunodeficiencies (e.g., as           |
| immunomodulation and                   | described below). Highly preferred     |
| differentiation and modulate T cell    | indications also include boosting a B  |
| proliferation and function.            | cell-mediated immune response and      |
| Exemplary assays that test for         | alternatively suppressing a B cell-    |
| immunomodulatory proteins evaluate     | mediated immune response. Highly       |
| the production of cytokines, such as   | preferred indications include          |
| IL-6, and the stimulation and          | inflammation and inflammatory          |
| upregulation of T cell proliferation   | disorders. Additional highly preferred |
| and functional activities. Such        | indications include asthma and         |
| assays that may be used or routinely   | allergy. Highly preferred indications  |
| modified to test immunomodulatory      | include neoplastic diseases (e.g.,     |
| and diffferentiation activity of       | myeloma, plasmacytoma, leukemia,       |
| polypeptides of the invention          | lymphoma, melanoma, and/or as          |
| (including antibodies and agonists or  | described below under                  |
| antagonists of the invention) include  | "Hyperproliferative Disorders").       |
| assays disclosed in Miraglia et al., J | Highly preferred indications include   |
| Biomolecular Screening 4:193-          | neoplasms and cancers, such as,        |
| 204(1999); Rowland et al.,             | myeloma, plasmacytoma, leukemia,       |
| "Lymphocytes: a practical approach"    | lymphoma, melanoma, and prostate,      |
| Chapter 6:138-160 (2000); and          | breast, lung, colon, pancreatic,       |
| Verhasselt et al., J Immunol           | esophageal, stomach, brain, liver and  |
| 158:2919-2925 (1997), the contents     | urinary cancer. Other preferred        |
| of each of which are herein            | indications include benign             |
| incorporated by reference in its       | dysproliferative disorders and pre-    |
| entirety. Human dendritic cells that   | neoplastic conditions, such as, for    |
| may be used according to these         | example, hyperplasia, metaplasia,      |
| assays may be isolated using           | and/or dysplasia. Preferred            |
| techniques disclosed herein or         | indications include anemia,            |
| otherwise known in the art. Human      | pancytopenia, leukopenia,              |

| I thrombocytopenii, Hodgkiri, et dissee, aute lymphocyte anenie (ALL), mrlipte myotoma. Burkiri symphoma, et myotoma, burkiri symphoma, et missa, AIDS, gamuhomatous disseae, inflammatony howed tiessee, spissis, neuropenia, roetneophiia, poetisis, suppression organis, and the commer restories to transplanted organs and itsuse, kernophila, poetisis, and the conformation of miderion in friend in different difficulties in friendin (i.g., an infection dissease as described below midericitous disseases. In additional proferred indication is infection (i.g., an infection dissease as described below mider "lifectious Disseas"). | A highly pretirent indication is diabetes mellinas.  A highly pretirent indication is a complication pretirent indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic retinopathy, diabetic retinopathy is diabetic retinopathy is diabetic retinopathy and adverted reasons and disabetic retinopathy and about the fall fall fall fall fall fall fall fal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| dendrific cells are artigen presenting<br>left in suspension colline, which,<br>when activated by artigen and/or<br>software and interest and or<br>cell polification and functional<br>activities.                                                                                                                                                                                                                                                                                                                                                                                                                                                 | transarption of Malie Enzyma ere well-known in the art and may be used or remissription of Malie Enzyma ere well-known in the art and may be used or remirnely modified to assess the eability of polyspeptides of the invention (totalufor authorities and againsts or entagonists of the invention) to replace transarption of Malie Enzyma, a key enzyma in Junetion) to regulate transarption of Malie Enzyma, is key enzyma in junovbed in lipogenesis and its recognist is stimulted by installin ME promotec contains two direct ME promotec contains two direct and ME dearlifed as putative PPAR response chements. ME promote remisserphion factors. Exemplary and ME dearlifed as putative PPAR response chements. ME promoter transarption factors. Exemplary and other transarption lactors. Exemplary modified to test for regulation of modified to test for regulation of |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | tragazinion of Malic<br>Enzyme in adipocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | £53                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HATBR65                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| disorders as described in the<br>"Cardiovascular Disorders" section<br>below), dyslipidemia, endocrine<br>disorders (as described in the<br>"Endocrine Disorders" section             | when, hethogram, vision impairment (e.g., diabetic retinopathy and ballionisses), lates and impaired wound healing, and infection (e.g., microins diseases and disorders as described in the "Infections and constitution of the unitra time and properties" of the unitra years and selected to of the unitra years and a Dayayters of the unitra years and properties of the propert | ed ir. catic catic clude clude weig                                                                                                                                                                                                                                                                                                                                                  | disheres realities, An additional highly preferred indication is a complication seed to the properties of the properties                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| invention (including antibodies and<br>agonisis or antagonisis of the<br>invention) include assays disclosed<br>in: Streeper, R.S., et al., Mol<br>Endocrinol, 12(11):1778-91 (1998); | Cardia-Infence, c., et al., Mobilitation of accordance of 1994).  Bridocrinol, 8(10);1361-9 (1994).  274(25);17997-8004 (1999).  274(25);17997-8004 (1999).  272(32);20106-20117 (1997).  and, Cullera, et al., Medinods in and confidence of the conf | incorporated by reference in its entirety. Hepatocyce last may be used according to these assays are used according to these assays are publicly available (e.g., through the ATCC**) and/or may be nouttinely address and/or may be nouttinely according to these used according to these than may be used according to these assays includes the HHIE rat liver hepatoms eed line. | A Assays for measuring secretion of<br>insulin are et ed-known in the art and<br>may be used or routinely modified in<br>may be used or routinely modified in<br>the invention (frolding ambodies of<br>the invention (frolding ambodies of<br>the invention) to simulate insulin<br>secretion; for example, insulin<br>secretion is measured by PMAT<br>insulin secretion from parezeatic bear<br>of six upregulated by glooses and<br>such is supregulated by the con-<br>tains of the contractive or the contractive or the<br>state of the contractive or the contractive or the<br>state of the contractive or the contractive or the contractive or the<br>state of the contractive or the contractive or the contractive or the<br>state of the contractive or the |
|                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                      | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                      | 424                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                      | HAUAI83                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                      | 50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| 7 - 7 | stroke, impotence (e.g., due to     | diabetic neuropainy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and       | disorders as described in the      | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the      | "Endocrine Disorders" section       | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious  | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's                   | contracture). An additional        | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. Additional | highly preferred indications are   | complications associated with insulin | resistance.                       |                                 |                                    |                                   |                                 |                                   |
|-------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|----------------------------------------|---------------------------------------------------|------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|----------------------------------------|------------------------------------|---------------------------------------|-----------------------------------|---------------------------------|------------------------------------|-----------------------------------|---------------------------------|-----------------------------------|
|       | disregulation is a key component in | madetes. Exemplary assays mat may   | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000); | Salapatek, A.M., et al., Mol       | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S et. al.,    | Journal of Biomolecular Screening,  | 4:193-204 (1999), the contents of   | each of which is herein incorporated | by reference in its entirety. | Pancreatic cells that may be used   | according to these assays are publicly | available (e.g., through the ATCC <sup>TM</sup> ) | and/or may be routinely generated. | Exemplary pancreatic cells that may    | be used according to these assays    | include HTTT15 Cells. HTTT15 are     | an adherent epithelial cell line   | established from Syrian hamster islet  | cells transformed with SV40. These | cells express glucagon, somatostatin, | and glucocorticoid receptors. The | cells secrete insulin, which is | stimulated by glucose and glucagon | and suppressed by somatostatin or | glucocorticoids. ATTC# CRL-1777 | Refs: Lord and Ashcroft. Biochem. |
|       |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                                   |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |
|       | _                                   |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                                   |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |

|    |         |     |                                          | J. 219: 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. |                                                                                               |
|----|---------|-----|------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 21 | HBAMB15 | 425 | Stimulation of insulin<br>secretion from | Assays for measuring secretion of insulin are well-known in the art and                | A highly preferred indication is diabetes mellitus.  An A |
|    |         |     | paneicane octa cens.                     | assess the ability of polypeptides of                                                  | accuronal inginy preferred increasion<br>is a complication associated with                    |
|    |         |     |                                          | the invention (including antibodies                                                    | diabetes (e.g., diabetic retinopathy,                                                         |
|    |         |     |                                          | and agonists or antagonists of the                                                     | diabetic nephropathy, kidney disease                                                          |
|    |         |     |                                          | invention) to stimulate insulin<br>secretion. For example, insulin                     | (e.g., renal failure, nephropathy<br>and/or other diseases and disorders as                   |
|    |         |     |                                          | secretion is measured by FMAT                                                          | described in the "Renal Disorders"                                                            |
|    |         |     |                                          | using anti-rat insulin antibodies.                                                     | section below), diabetic neuropathy,                                                          |
|    |         |     |                                          | Insulin secretion from pancreatic beta                                                 | nerve disease and nerve damage                                                                |
|    |         |     |                                          | cells is upregulated by glucose and                                                    | (e.g., due to diabetic neuropathy),                                                           |
|    |         |     |                                          | also by certain proteins/peptides, and                                                 | blood vessel blockage, heart disease,                                                         |
|    |         |     |                                          | disregulation is a key component in                                                    | stroke, impotence (e.g., due to                                                               |
|    |         |     |                                          | diabetes. Exemplary assays that may                                                    | diabetic neuropathy or blood vessel                                                           |
|    |         |     |                                          | be used or routinely modified to test                                                  | blockage), seizures, mental                                                                   |
|    |         |     |                                          | for stimulation of insulin secretion                                                   | confusion, drowsiness, nonketotic                                                             |
|    |         |     |                                          | (from pancreatic cells) by                                                             | hyperglycemic-hyperosmolar coma,                                                              |
|    |         |     |                                          | polypeptides of the invention                                                          | cardiovascular disease (e.g., heart                                                           |
|    |         |     |                                          | (including antibodics and agonists or                                                  | discase, atherosclerosis,                                                                     |
|    |         |     |                                          | antagonists of the invention) include                                                  | microvascular disease, hypertension,                                                          |
|    |         |     |                                          | assays disclosed in: Ahren, B., et al.,                                                | stroke, and other diseases and                                                                |
|    |         |     |                                          | Am J Physiol, 277(4 Pt 2):R959-66                                                      | disorders as described in the                                                                 |
|    |         |     |                                          | (1999); Li, M., et al., Endocrinology,                                                 | "Cardiovascular Disorders" section                                                            |
|    |         |     |                                          | 138(9):3735-40 (1997); Kim, K.H.,                                                      | below), dyslipidemia, endocrine                                                               |
|    |         |     |                                          | et al., FEBS Lett, 377(2):237-9                                                        | disorders (as described in the                                                                |
|    |         |     |                                          | (1995); and, Miraglia S ct. al.,                                                       | "Endocrine Disorders" section                                                                 |
|    |         |     |                                          | Journal of Biomolecular Screening,                                                     | below), neuropathy, vision                                                                    |
|    |         |     |                                          | 4:193-204 (1999), the contents of                                                      | impairment (e.g., diabetic retinopathy                                                        |
|    |         |     |                                          | each of which is herein incorporated                                                   | and blindness), ulcers and impaired                                                           |
|    |         |     |                                          | by reference in its entirety.                                                          | wound healing, and infection (e.g.,                                                           |
|    |         |     |                                          | Pancreatic cells that may be used                                                      | infectious diseases and disorders as                                                          |
|    |         |     |                                          | according to these assays are publicly                                                 | described in the "Infectious                                                                  |
|    |         |     |                                          | available (e.g., through the ATCCTM)                                                   | Diseases" section below, especially                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | illigh V highly preferred indication is are diabetes mellins. An additional are diabetes mellins. An additional are diabetes mellins associated with diabetes occupied with a diabetes respinopathy, kidney disease (e.g., renal failure, replinopathy and andice other diseases and mere diamage each become an accordance of a diabetic neuropathy or blood vessel bloodega, hearines, mental confliction, diseases, in propersision, drowstatus es association of diabetic neuropathy or blood vessel bloodega, hearines, montal confliction, drowstatus es association diversists, nonzectorie hyperegly-owned-typersonal-organic processes, in precesses and diseases, and dure diseases, and dure diseases, and dure diseases, and earned and described in the BM. "Cardforwacular Disorders" section in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Randor may be routinely generated.  Randpalo protectic cells falte may be used acousting to these assays the class of the | Assays for the regulation of vibility and polification of cells in vitro are used-tensor in the art and may be used or routinely modified to assess the shility of polyperpides of the invention (including anthedreis and agonists or antagonists of the provided polyperpides of the invention) to regulate vibility and polyfication of pancratic beta cells. In custance, the Cell Three-fol luminescent cell viability assay in culture based on quantitation of measures the number of visible cells in culture based on quantitation of the ATP present which signals the presence of methodically active profileration of viability and active the profileration of viability and active the method of the invention of viability and calculating antidoxis and geomiss or damagoniss of the invention included antigoniss of the invention included antigoniss of the invention in cluded antigoniss of the invention of the profession of the profession of the profession of the profession of the invention of the preserved of the invention of the cluded antigonism of the profession of the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Regulation of vibility<br>Regulation of panorestic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 426                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HBGBA69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | ដ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                   | (2001); Huotari MA, et al.,             | below), dyslipidemia, endocrine        |
|----|---------|-----|-------------------|-----------------------------------------|----------------------------------------|
|    |         |     |                   | Endocrinology, 139(4):1494-9            | disorders (as described in the         |
|    |         |     |                   | (1998); Hugl SR, et al., J Biol Chem    | "Endocrine Disorders" section          |
|    |         |     |                   | 1998 Jul 10;273(28):17771-9 (1998),     | below), neuropathy, vision             |
|    |         |     |                   | the contents of each of which is        | impairment (e.g., diabetic retinopathy |
|    |         |     |                   | herein incorporated by reference in     | and blindness), ulcers and impaired    |
|    |         |     |                   | its entirety. Pancreatic cells that may | wound healing, and infection (e.g.,    |
|    |         |     |                   | be used according to these assays are   | infectious diseases and disorders as   |
|    |         |     |                   | publicly available (e.g., through the   | described in the "Infectious           |
|    |         |     |                   | ATCCTM) and/or may be routinely         | Diseases" section below, especially    |
|    |         |     |                   | generated. Exemplary pancreatic         | of the urinary tract and skin), carpal |
|    |         |     |                   | cells that may be used according to     | tunnel syndrome and Dupuytren's        |
|    |         |     |                   | these assays include rat INS-1 cells.   | contracture). An additional highly     |
|    |         |     |                   | INS-1 cells are a semi-adherent cell    | preferred indication is obesity and/or |
|    |         |     |                   | line established from cells isolated    | complications associated with          |
|    |         |     |                   | from an X-ray induced rat               | obesity. Additional highly preferred   |
|    |         |     |                   | transplantable insulinoma. These        | indications include weight loss or     |
|    |         |     |                   | cells retain characteristics typical of | alternatively, weight gain. Additional |
|    |         |     |                   | native pancreatic beta cells including  | highly preferred indications are       |
|    |         |     |                   | glucose inducible insulin secretion.    | complications associated with insulin  |
|    |         |     |                   | References: Asfari et al.               | resistance.                            |
|    |         |     |                   | Endocrinology 1992 130:167.             |                                        |
|    | HBGNU56 | 427 | Activation of     | Kinase assay. Kinase assays, for        | A highly preferred embodiment of       |
| 23 |         |     | Hepatocyte ERK    | example an Elk-1 kinase assay, for      | the invention includes a method for    |
|    |         |     | Signaling Pathway | ERK signal transduction that regulate   | stimulating hepatocyte cell            |
|    |         |     |                   | cell proliferation or differentiation   | proliferation. An alternative highly   |
|    |         |     |                   | are well known in the art and may be    | preferred embodiment of the            |
|    |         |     |                   | used or routinely modified to assess    | invention includes a method for        |
|    |         |     |                   | the ability of polypeptides of the      | inhibiting hepatocyte cell             |
|    |         |     |                   | invention (including antibodies and     | proliferation. A highly preferred      |
|    |         |     |                   | agonists or antagonists of the          | embodiment of the invention            |
|    |         |     |                   | invention) to promote or inhibit cell   | includes a method for stimulating      |
|    |         |     |                   | proliferation, activation, and          | hepatocyte cell differentiation. An    |
|    |         |     |                   | differentiation. Exemplary assays for   | alternative highly preferred           |
|    |         |     |                   | ERK kinase activity that may be used    | embodiment of the invention            |
|    |         |     |                   | or routinely modified to test ERK       | includes a method for inhibiting       |
|    |         |     |                   | kinase-induced activity of              | hepatocyte cell differentiation. A     |

| highly preferred embodiment of the invention includes a method for activating hepatocyte cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the                              | activation of and/or inactivating hepatocyte cells. Highly preferred indications include disorders of the liver and/or endocrate disorders (e.g., as described below under "Indocrine Disorders"). Preferred indications include reoplastic diseases (e.g., as described below under "Indocrine disorders"). | hyperpoliterator Disorders"),<br>blood disorders (e.g., as described<br>blood disorders (e.g., as described<br>blood wider "lummer Activity",<br>"Cardiovascular Disorders", immune<br>disorders (e.g., as described below<br>under "Immune Activity"), neural<br>disorders (e.g., as described below<br>under "Immune Activity"), neural<br>under "Parial Activity").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | infection (e.g., as desarribed below methods and offer infection (e.g., as desarribed below methods in the control of the cont |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| polypeptides of the invention<br>(including antibodies and agonists or<br>antagonists of the invention) include<br>the assays disclosed in Forrer et al.,<br>Biol Chem 379(8-9);1101-1110<br>(1998); Kyriakis JM, Biochem Soc | Symple 429-48 (1999); Chang and<br>Karin, Nature 410(6824);37-40<br>(2001); and Cobb MH, Prog Biophys<br>Most Biol 71(64-329-500 (1999);<br>the centents of each of which are<br>herein incorporated by reference in<br>its entirey. Rat liver tepatomn cells<br>that may be used according to these         | through the ATCC <sup>19</sup> . Exemplary through the ATCC <sup>19</sup> . Exemplary in Priter Department of elit that may be used according to these assets are proposed according to these assets of the account to the account of the acco |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|   |  | (e.g., due to diabetic neuropathy),    |
|---|--|----------------------------------------|
|   |  | blood vessel blockage, heart disease,  |
|   |  | stroke, impotence (e.g., due to        |
|   |  | diabetic neuropathy or blood vessel    |
|   |  | blockage), seizures, mental            |
|   |  | confusion, drowsiness, nonketotic      |
|   |  | hyperglycemic-hyperosmolar coma,       |
|   |  | cardiovascular disease (e.g., heart    |
|   |  | disease, atherosclerosis,              |
|   |  | microvascular disease, hypertension,   |
|   |  | stroke, and other diseases and         |
|   |  | disorders as described in the          |
|   |  | "Cardiovascular Disorders" section     |
|   |  | below), dyslipidemia, endocrine        |
|   |  | disorders (as described in the         |
|   |  | "Endocrine Disorders" section          |
|   |  | below), neuropathy, vision             |
|   |  | impairment (e.g., diabetic retinopathy |
|   |  | and blindness), ulcers and impaired    |
|   |  | wound healing, infection (e.g.,        |
|   |  | infectious diseases and disorders as   |
|   |  | described in the "Infectious           |
|   |  | Diseases" section below, especially    |
|   |  | of the urinary tract and skin), carpal |
|   |  | tunnel syndrome and Dupuytren's        |
|   |  | contracture). An additional highly     |
|   |  | preferred indication is obesity and/or |
|   |  | complications associated with          |
|   |  | obesity. Additional highly preferred   |
|   |  | indications include weight loss or     |
|   |  | alternatively, weight gain.            |
|   |  | Additional highly preferred            |
|   |  | indications are complications          |
|   |  | associated with insulin resistance.    |
|   |  | Additional highly preferred            |
|   |  | indications are disorders of the       |
| _ |  | musculoskeletal systems including      |

|    |         |     |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | myopathies, muscular dystrophy, andor as described herein. Additional highly preferred indications include, hepatitis, almandice, gallstones, cirribosas of the liver, degenerative or necrotic liver.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----|---------|-----|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |         |     |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | disease, alcoholic liver diseases, fibousis, liver regeneration, metabolic disease, dyslipidemia and ehlolesteror metabolism. Additional highly preferred midcations include mooplasms and ennees, such as heppidocarcinomas, and return and advanced and control in the second and advanced and midcations include mooplasms and ennees, such as heppidocarcinomas, and advanced |
|    |         |     |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | pancrenic cancer. Preferred micrations salso include prostate, breas, lung, esophageal, somach, brand, and ulmary, accord. Other preferred indications include benign preferred indications include benign nonylastic conditions, such as, for nonylastic conditions, such as, for anylangic properlists, metaplasis, and/ar dysopeplasis, metaplasis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 24 | HBIAE26 | 428 | Insulin Secretion | Assays for measuring secretion of maining are well-known in the art and may be used or routinely modified to the property of the property of the invention (including ambrodies of the invention to simulate institution and acceptance of the invention) to simulate institution secretion. For example, insulin secretion is measured by PMAT using anti-art insulin anti-old-disting anti-old-disting anti-old-disting anti-old-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting-disting | A highly preferred indication is indicated in the discovered indication is a highly preferred indication is a highly preferred indication is a nonpication associated with diabetes (e.g., diabetic retinopathy, kidney disease (e.g., diabetic retinopathy, kidney disease (e.g., creal failure, rephropathy, kidney disease (e.g., creal failure, rephropathy, and/or other diseases and disorders as section in the "Mean Disorders as section in the "Nature Disorders" as section below, diabetic neuropathy, exclude the article of the "Nature Canage and clientic neuropathy, ediabetic neuropathy, ediabe |
|    |         |     |                   | also by certain proteins/peptides, and<br>disregulation is a key component in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | blood vessel blockage, heart disease,<br>stroke, impotence (e.g., due to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| _                                   |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |                                                          |
|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|----------------------------------------|--------------------------------------|------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|----------------------------------------|------------------------------------|---------------------------------------|-----------------------------------|---------------------------------|------------------------------------|-----------------------------------|---------------------------------|-----------------------------------|----------------------------------------------------------|
| diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and       | disorders as described in the      | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the      | "Endocrine Disorders" section       | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious  | Diseases" section below, especially | of the urinary tract and skin), carpal | me a                                 | contracture). An additional        | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. Additional | highly preferred indications are   | complications associated with insulin | resistance.                       |                                 |                                    |                                   |                                 |                                   |                                                          |
| diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000); | Salapatek, A.M., et al., Mol       | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S et. al.,    | Journal of Biomolecular Screening,  | 4:193-204 (1999), the contents of   | each of which is herein incorporated | by reference in its entirety. | Pancreatic cells that may be used   | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary pancreatic cells that may    | be used according to these assays    | include HITT15 Cells. HITT15 are     | an adherent epithelial cell line   | established from Syrian hamster islet  | cells transformed with SV40. These | cells express glucagon, somatostatin, | and glucocorticoid receptors. The | cells secrete insulin, which is | stimulated by glucose and glucagon | and suppressed by somatostatin or | glucocorticoids. ATTC# CRL-1777 | Refs: Lord and Ashcroft. Biochem. | <ul><li>J. 219: 547-551; Santerre et al. Proc.</li></ul> |
|                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |                                                          |
|                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |                                                          |
| 1                                   |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |                                                          |

|                                              | A highly preferred embodiment for shmaling adipocyte the invention includes a method for shmalining adipocyte preferred embodiment of the preferred embodiment of the inhibiting adipocyte proliferation.  A highly preferred embodiment of the the invention includes a method for inhibiting adipocyte proliferation.  An alternative bighly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation.  An alternative bighly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation.  An alternative bighly preferred invention includes a method for control of the invention includes a method for intellibiting adipocyte activation. An alternative includes a method of or invention includes a method for for invention includes a method of or invention includes a method of or invention includes as method for invention includes as method of decreasing) and/or inactivation of (e.g., as described below indications include and/or as descreasing) and/or inactivation indications include and/or as descreasing and/or and/or as descreasing and/or and/or as descreasing and/or and/or as deferred adications include bolod disorders (e.g., hypertension, and/or as descreasing hand, and as a method or indicates hand and as a method or as deferred adications include bolod disorders (e.g., hypertension, include bolod disorders (e.g., hypertension, and/or as hand disorders (e.g., hypertension, and/or as descreasing) and/or as hand disorders (e.g., hypertension, and/or as descreasing and/or as hand disorders (e.g., hypertension, and/or as descreasing and/or as hand disorders (e.g., hypertension, and/or as descreasing and/or as hand disorders (e.g., hypertension, and/or as decreasing and/or as hand disorders (e.g., hypertension, and/or as decreasing and/or as hand disorders (e.g., hypertension, and/or as decreasing and/or as hand disorders (e.g., hypertension, and/or as                                                                                                            |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | Kinnse ussay, Kinnee assays, for exemple at IR-1 kinnee assays, for exemple at IR-1 kinnee assay, for IR-R sgoal transduction that regulated are well known in the art and may be a proposed or requirely modified to assess the shifty of polypeptides of the interaction (including antibodies and agonists or antagonists of the articular proposed activity of hearthy for known extravioral or promotion en inhibit cell prolification, activation, and fulficentiation. Exemplary assays for ERK knows extrivity of hearthy breaded or rouninely modified to test RRK knows extrivity of hearthy for his exemplary assays for PRK knows extrivity of hearthy for his exemplary and interaction or rouninely modified to test RRK knows extrivity of hearthy for his exemplary modified to test RRK banes extravity of hearthy exemples and good or nonlinely modified to test RRK Brancocknot of the invention include antagonists of the invention include antagonists of the invention include antagonists of the invention includes antagonists of the invention included antagonists of the invention of the proposed of the invention of the following the APC (2011) and Cobb MII. Poly Biophys Mod Biol 71(3-15-45-500 (1993)); the contents of each of which are become entirely. Monuse adipocyte cells that the transport of the APC expenses in its entirety. Monuse adipocyte cells that was been assays are publicly available to g., in any and the season assays are publicly variable to g., and the season assays are publicly variable to g., and assay are publicly variable to g., and and assay are publicly variable to g., and assay are publicly variable to g., and and assay a |
|                                              | Activation of Adipocyte ERK Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                              | 430                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                              | HBJFU48                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                              | 58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| used ac  | used according to these assays<br>include 3T3-L1 cells. 3T3-L1 is an | impotence and/or as described below<br>under "Immune Activity", |
|----------|----------------------------------------------------------------------|-----------------------------------------------------------------|
| adhero   | adherent mouse preadipocyte cell                                     | "Cardiovascular Disorders", and/or                              |
| line the | line that is a continuous substrain of                               | "Blood-Related Disorders"), immune                              |
| through  | through clonal isolation and undergo                                 | under "Immune Activity"), neural                                |
| a pre-a  | a pre-adipocyte to adipose-like                                      | disorders (e.g., as described below                             |
| conver   | conversion under appropriate                                         | under "Neural Activity and                                      |
| differen | differentiation conditions known in                                  | Neurological Diseases"), and                                    |
| the art. |                                                                      | infection (e.g., as described below                             |
|          |                                                                      | under "Infectious Disease").                                    |
|          |                                                                      | ji                                                              |
|          |                                                                      | diabetes mellitus. An additional                                |
|          |                                                                      | highly preferred indication is a                                |
|          |                                                                      | complication associated with                                    |
|          |                                                                      | diabetes (e.g., diabetic retinopathy,                           |
|          |                                                                      | diabetic nephropathy, kidney disease                            |
|          |                                                                      | (e.g., renal failure, nephropathy                               |
|          |                                                                      | and/or other diseases and disorders as                          |
|          |                                                                      | described in the "Renal Disorders"                              |
|          |                                                                      | section below), diabetic neuropathy,                            |
|          |                                                                      | nerve disease and nerve damage                                  |
|          |                                                                      | (e.g., due to diabetic neuropathy),                             |
|          |                                                                      | blood vessel blockage, heart disease,                           |
|          |                                                                      | stroke, impotence (e.g., due to                                 |
|          |                                                                      | diabetic neuropathy or blood vessel                             |
|          |                                                                      | blockage), seizures, mental                                     |
|          |                                                                      | confusion, drowsiness, nonketotic                               |
|          |                                                                      | hyperglycemic-hyperosmolar coma,                                |
|          |                                                                      | cardiovascular disease (e.g., heart                             |
|          |                                                                      | disease, atherosclerosis,                                       |
|          |                                                                      | microvascular disease, hypertension,                            |
|          |                                                                      | stroke, and other diseases and                                  |
|          |                                                                      | disorders as described in the                                   |
|          |                                                                      | "Cardiovascular Disorders" section                              |
|          |                                                                      | below), dyslipidemia, endocrine                                 |
|          |                                                                      | disorders (as described in the                                  |

|  |  | "Fndocrine Disorders" section           |
|--|--|-----------------------------------------|
|  |  | halour) namonathy vision                |
|  |  | below), neuropamy, vision               |
|  |  | impairment (e.g., diabetic retinopathy  |
|  |  | and blindness), ulcers and impaired     |
|  |  | wound healing, infection (e.g.,         |
|  |  | infectious diseases and disorders as    |
|  |  | described in the "Infectious            |
|  |  | Diseases" section below (particularly   |
|  |  | of the urinary tract and skin). An      |
|  |  | additional highly preferred indication  |
|  |  | is obesity and/or complications         |
|  |  | associated with obesity. Additional     |
|  |  | highly preferred indications include    |
|  |  | weight loss or alternatively, weight    |
|  |  | gain. Additional highly                 |
|  |  | g                                       |
|  |  | complications associated with insulin   |
|  |  | resistance. Additional highly           |
|  |  | preferred indications are disorders of  |
|  |  | the musculoskeletal systems             |
|  |  | including myopathies, muscular          |
|  |  | dystrophy, and/or as described          |
|  |  | herein. Additional highly               |
|  |  | preferred indications include,          |
|  |  | hypertension, coronary artery           |
|  |  | disease, dyslipidemia, gallstones,      |
|  |  | osteoarthritis, degenerative arthritis, |
|  |  | eating disorders, fibrosis, cachexia,   |
|  |  | and kidney diseases or disorders.       |
|  |  | Preferred indications include           |
|  |  | neoplasms and cancer, such as,          |
|  |  | lymphoma, leukemia and breast,          |
|  |  | colon, and kidney cancer. Additional    |
|  |  | preferred indications include           |
|  |  | melanoma, prostate, lung,               |
|  |  | pancreatic, esophageal, stomach,        |
|  |  | brain, liver, and urinary cancer.       |

|    |         |     |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | rugin, preterret uniqualons include lipomas and liposarcomas. Other preferred indications include benigh dysproliferative disorders and pre-repoplastic conditions, such as, for example, hyperplasis, metaplasia, and ord vysplasia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----|---------|-----|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 92 | HBJFU48 | 430 | Production of IL-6 | cells and has stong effects only per cells and has stong effects only per cells. In 6 participates in IL-4 induced up from the cells. IL-6 participates in IL-4 induced up from the cells. IL-6 participates in IL-4 moused immunity. IL-6 induces by moused immunity. IL-6 induces cytoloxic of Cells. Dergelland of expression of IL-6 has been linked to autoinnume disease, pleasure of many per cells. Dergelland or proteins by perpositicative diseases. Assays from IL-6 has been linked to autoinnume disease, pleasured or has per profession of IL-6 has been linked to hyperpoliteative diseases. Assays from time non-delineary and differentiation factor proteins produced by a large variety of cells where the expression leed is strongly regulated by cytolkines, growth from the art and may be used or regulated by cytolkines, growth and may be used or manifely medified and may be used or anterior in cludinging authorides and agonists of the immunomodulation and differentiation and modulate I cell immunomodulation and differentiation of cytokines, such as the production of cytokines, such as | the highly profered enhodiment of the invention includes a mothed for simulating (e.g., increasing) IL-6 reports on the dependent of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. An alleghy preferred indication is the simulation or enhancement of innexes in immunity. Highly preferred indication is the simulation or enhancement of innexes in immunity. Highly preferred indications include below under "immune solitation" in the simulation or enhancement of mode sinchesters (e.g., as described below under "immune prisentes"; and or "infection" (e.g., as described below under "infections 15 seases"). Highly preferred indications include of the common of arthritis, systemic lupus preferred indications include of the control arthritis, systemic lupus exercibed below). Highly preferred indications also include bosoting a Bidescribed below). Highly preferred indications also include bosoting a Bidescribed below). Highly preferred indications also include bosoting a Bidescribed below. Highly preferred indications also include bosoting a Bidescribed below). Highly preferred indications also include bosoting a Bidescribed below. Highly preferred indications also include bosoting a Bidescribed below. Highly preferred indications also include bosoting a Bidescribed below. Highly preferred indications include proposition include preferred indications include proposition include preferred indications include proposition included prampared response. |

| upregulation of T cell proliferation assays that may be used or routinely modified to test immunomobilatory and diffreentiation activity of properties of the invention include angonists of the invention include assays disclosed in Miragita et al., 1944 (1995); Rowland et al., 204(1995); Rowland et al., 204(1997), the contents of each of which are bettern incorporated by reference in its effect of which better in the experimental according to these seasons may be used according to these cases may be isabled using experimental and according to these decidic cells are antigen presenting dendric cells are antigen under which when activated by antigen and opergradue? |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| a s s s s s s s s s s s s s s s s s s s                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |

|    | HBJLC01 | 431 | Activation of        | Kinase assav. Kinase assavs. for       | A hiehly preferred embodiment of       |
|----|---------|-----|----------------------|----------------------------------------|----------------------------------------|
| 27 |         |     | Adipocyte PI3 Kinase | example an GSK-3 assays, for PI3       | the invention includes a method for    |
|    |         |     | Signalling Pathway   | kinase signal transduction that        | increasing adipocyte survival An       |
|    |         |     |                      | regulate glucose metabolism and cell   | alternative highly preferred           |
|    |         |     |                      | survival are well-known in the art     | embodiment of the invention            |
|    |         |     |                      | and may be used or routinely           | includes a method for decreasing       |
|    |         |     |                      | modified to assess the ability of      | adipocyte survival. A preferred        |
|    |         |     |                      | polypeptides of the invention          | embodiment of the invention            |
|    |         |     |                      | (including antibodies and agonists or  | includes a method for stimulating      |
|    |         |     |                      | antagonists of the invention) to       | adipocyte proliferation. An            |
|    |         |     |                      | promote or inhibit glucose             | alternative highly preferred           |
|    |         |     |                      | metabolism and cell survival.          | embodiment of the invention            |
|    |         |     |                      | Exemplary assays for PI3 kinase        | includes a method for inhibiting       |
|    |         |     |                      | activity that may be used or routinely | adipocyte proliferation. A             |
|    |         |     |                      | modified to test PI3 kinase-induced    | preferred embodiment of the            |
|    |         |     |                      | activity of polypeptides of the        | invention includes a method for        |
|    |         |     |                      | invention (including antibodies and    | stimulating adipocyte differentiation. |
|    |         |     |                      | agonists or antagonists of the         | An alternative highly preferred        |
|    |         |     |                      | invention) include assays disclosed in | embodiment of the invention            |
|    |         |     |                      | Forrer et al., Biol Chem 379(8-        | includes a method for inhibiting       |
|    |         |     |                      | 9):1101-1110 (1998); Nikoulina et      | adipocyte differentiation. Highly      |
|    |         |     |                      | al., Diabetes 49(2):263-271 (2000);    | preferred indications include          |
|    |         |     |                      | and Schreyer et al., Diabetes          | endocrine disorders (e.g., as          |
|    |         |     |                      | 48(8):1662-1666 (1999), the contents   | described below under "Endocrine       |
|    |         |     |                      | of each of which are herein            | Disorders"). Preferred indications     |
|    |         |     |                      | incorporated by reference in its       | include neoplastic diseases (e.g.,     |
|    |         |     |                      | entirety. Mouse adipocyte cells that   | lipomas, liposarcomas, and/or as       |
|    |         |     |                      | may be used according to these         | described below under                  |
|    |         |     |                      | assays are publicly available (e.g.,   | "Hyperproliferative Disorders"),       |
|    |         |     |                      | through the ATCCTM). Exemplary         | blood disorders (e.g., hypertension,   |
|    |         |     |                      | mouse adipocyte cells that may be      | congestive heart failure, blood vessel |
|    |         |     |                      | used according to these assays         | blockage, heart disease, stroke,       |
|    |         |     |                      | include 3T3-L1 cells. 3T3-L1 is an     | impotence and/or as described below    |
|    |         |     |                      | adherent mouse preadipocyte cell       | under "Immune Activity",               |
|    |         |     |                      | line that is a continous substrain of  | "Cardiovascular Disorders", and/or     |
|    |         |     |                      | 3T3 fibroblast cells developed         | "Blood-Related Disorders"), immune     |
|    |         |     |                      | through clonal isolation and undergo   | disorders (e.g., as described below    |

| a pre-adipocyte to adipose-like     |      | under "Immune Activity"), neural       |
|-------------------------------------|------|----------------------------------------|
| conversion under appropriate        |      | disorders (e.g., as described below    |
| differentiation conditions known in | _    | under "Neural Activity and             |
| the art.                            | Nen  | Neurological Diseases"), and           |
|                                     | infe | infection (e.g., as described below    |
|                                     | pun  | inder "Infectious Disease"). A         |
|                                     | high | highly preferred indication is         |
|                                     | diah | diabetes mellitus. An                  |
|                                     | addi | additional highly preferred indication |
|                                     | isa  | s a complication associated with       |
|                                     | diab | diabetes (e.g., diabetic retinopathy,  |
|                                     | diah | diabetic nephropathy, kidney disease   |
|                                     | (e.g | e.g., renal failure, nephropathy       |
|                                     | pue  | and/or other diseases and disorders as |
|                                     | desc | described in the "Renal Disorders"     |
|                                     | sect | section below), diabetic neuropathy,   |
|                                     | ner  | nerve disease and nerve damage (e.g.,  |
|                                     | due  | due to diabetic neuropathy), blood     |
|                                     | vess | vessel blockage, heart disease,        |
|                                     | orts | stroke, impotence (e.g., due to        |
|                                     | diab | diabetic neuropathy or blood vessel    |
|                                     | ploc | olockage), seizures, mental            |
|                                     | con  | confusion, drowsiness, nonketotic      |
|                                     | dáq  | hyperglycemic-hyperosmolar coma,       |
|                                     | card | cardiovascular disease (e.g., heart    |
|                                     | disc | disease, atherosclerosis,              |
|                                     | mic  | microvascular disease, hypertension,   |
|                                     | stro | stroke, and other diseases and         |
|                                     | osip | disorders as described in the          |
|                                     | Ca   | "Cardiovascular Disorders" section     |
|                                     | pelo | below), dyslipidemia, endocrine        |
|                                     | diso | disorders (as described in the         |
|                                     |      | "Endocrine Disorders" section          |
|                                     | pelo | below), neuropathy, vision             |
|                                     | dini | impairment (e.g., diabetic retinopathy |
|                                     | and  | and blindness), ulcers and impaired    |
|                                     | NOU  | wound healing, infection (e.g.,        |

| _ |  | infectious diseases and disorders as    |
|---|--|-----------------------------------------|
|   |  | described in the "Infections            |
|   |  | Diseases" section below, especially     |
|   |  | of the urinary tract and skin), carpal  |
|   |  | tunnel syndrome and Dupuytren's         |
|   |  | contracture). An additional             |
|   |  | highly preferred indication is obesity  |
|   |  | and/or complications associated with    |
|   |  | obesity. Additional highly preferred    |
|   |  | indications include weight loss or      |
|   |  | alternatively, weight gain.             |
|   |  | Additional highly preferred             |
|   |  | indications are complications           |
|   |  | associated with insulin resistance.     |
|   |  | Additional highly preferred             |
|   |  | indications are disorders of the        |
|   |  | musculoskeletal systems including       |
|   |  | myopathies, muscular dystrophy,         |
|   |  | and/or as described herein.             |
|   |  | Additional highly preferred             |
|   |  | indications include, hypertension,      |
|   |  | coronary artery disease,                |
|   |  | dyslipidemia, gallstones,               |
|   |  | osteoarthritis, degenerative arthritis, |
|   |  | eating disorders, fibrosis, cachexia,   |
|   |  | and kidney diseases or disorders.       |
|   |  | Highly preferred indications include    |
|   |  | neoplasms and cancer, such as,          |
|   |  | lipoma, liposarcoma, lymphoma,          |
|   |  | leukemia and breast, colon, and         |
|   |  | kidney cancer. Additional highly        |
|   |  | preferred indications include           |
|   |  | melanoma, prostate, lung,               |
|   |  | pancreatic, esophageal, stomach,        |
|   |  | brain, liver, and urinary cancer.       |
|   |  | Other preferred indications include     |
|   |  | benign dysproliferative disorders and   |

| pre-neoplastic conditions, such as,<br>for example, hyperplasia, metaplasia,<br>and/or dysplasia. | A highly preferred indication is | obesity and/or complications   | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. An additional highly preferred | indication is diabetes mellitus. An   | additional highly preferred indication | is a complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy   | and/or other diseases and disorders as | described in the "Renal Disorders"    | section below), diabetic neuropathy, | nerve disease and nerve damage      | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to       | diabetic neuropathy or blood vessel | blockage), seizures, mental        | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma,     | cardiovascular disease (e.g., heart | disease, atherosclerosis,    | microvascular disease, hypertension, | stroke, and other diseases and        | disorders as described in the         | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section        | below), neuropathy, vision      | impairment (e.g., diabetic retinopathy |
|---------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|----------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|------------------------------------|------------------------------------|--------------------------------------|-------------------------------------|------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|--------------------------------|--------------------------------------|---------------------------------|----------------------------------------|
|                                                                                                   | Assays for the activation of     | transcription through the cAMP | response element are well-known in  | the art and may be used or routinely | modified to assess the ability of    | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) to       | increase cAMP, regulate CREB      | transcription factors, and modulate   | expression of genes involved in a    | wide variety of cell functions. For | example, a 3T3-L1/CRE reporter         | assay may be used to identify factors | that activate the cAMP signaling     | pathway. CREB plays a major role in | adipogenesis, and is involved in    | differentiation into adipocytes. CRE  | contains the binding sequence for the | transcription factor CREB (CRE      | binding protein). Exemplary assays | for transcription through the cAMP | response element that may be used or | routinely modified to test cAMP-    | response element activity of | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol       | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Reusch et al., Mol Cell   |
|                                                                                                   | Activation of                    | transcription through          | cAMP response                       | element (CRE) in pre-                | adipocytes.                          |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                       |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                      |                                     |                              |                                      |                                       |                                       |                                    |                                 |                                |                                      |                                 |                                        |
|                                                                                                   | 431                              |                                |                                     |                                      |                                      |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                       |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                      |                                     |                              |                                      |                                       |                                       |                                    |                                 |                                |                                      |                                 |                                        |
|                                                                                                   | HBJLC01                          |                                |                                     |                                      |                                      |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                       |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                      |                                     |                              |                                      |                                       |                                       |                                    |                                 |                                |                                      |                                 |                                        |
|                                                                                                   | -                                | 27                             |                                     |                                      |                                      |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                       |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                      |                                     |                              |                                      |                                       |                                       |                                    |                                 |                                |                                      |                                 |                                        |

| and blindness), utoers and impaired would heling, and infection (e.g., infections diseases and disorders as Diseases' section below, especially of the utilinary teat and skin), carpal tunnel syndrome and Dispoyten's preferred infections are more complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Preferred indications include neopolastic diseases (e. 24 accasedhow under "Hipperpoliteration"). Bisancher, Bosonder, Bosonde                                                                                                                                   |
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| Biol 20(2); 1008-1020 (2000); and feterm et al., 2180 (Chem 2739)7-97-923 (1998), the contents of each of which are brein incorporated by reference in its entirety. Prevention is entirety. Prevention in sentirety. Prevention of the contents of the conten | transacription through the AP I<br>transacription through the AP I<br>stood section through the AP I<br>stood section are frawn in the<br>art and may be used or routinely<br>modified to assess the ability of<br>poperprises of the invention to<br>modulate growth and other cell<br>function. Exemplary assays for<br>transacription through the AP I<br>transacription and other cell<br>transacription and other cell<br>modulated and other cell<br>transacription and other cell<br>modulated and other cell<br>transacription and other cell<br>transacription and other cell<br>transacription and other cell<br>modulated and the cell<br>polypeptides of the invention<br>(conclusing analyses and geomists or<br>authorises of the invention<br>(conclusion and conclusion and geometric<br>properties of the invention<br>(conclusion and conclusion and conclusion<br>and conclusion and conclusion<br>(conclusion and conclusi |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of Ac                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 491                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HBJLC01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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|         |     |                    | Gaes des Liste (1988). Culten and Malm, Methods in Engrer et al., Gaes des 1-10 (1988). Culten and Malm, Methods in Enzymol. Proc. 18-62-586 (1992). Heathmer et al., Proc. Neal Acad Sci. USA, 85:6342. Chem. 272(49):2086-3081 (1997). Ghem. 272(49):2086-3081 (1997). Asket-4993 (1998), and Fruser et al., Bur I Immunol. 29(3):888-844 (1999), the contents of each of which the process of the contents of each of which the process of the contents of each of which of the process of the contents of each of which in Securiory. Teels that may be used according to these used according to these used according to these used according to these assays include the CTLL cell line. ATCC "10. Escription process of the season assays include the CTLL cell line. Suppreprint of the process of the content of the process of the season assays include the CTLL cell line. Suppreprint of the season assays include the CTLL cell line. Suppreprint of the season assays include the CTLL cell line. Suppreprint of the season assays include the CTLL cell line. Suppreprint of the season according to the seaso | preferred indications include Information and informanosy disorders. Highly preferred information and information and information and include tooplastic discusses (e.g., leukenina, jumphoma, and ora el described below under "Hyperpoiliferative Disorders"). "Hyperpoiliferative Disorders"). Highly preferred inforations include neoplasers and emerce, satch as, the discussion include breight of the control of th |
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|         |     |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | immune reactions to transplanted organs and tissues, endocarditis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| HBJLC01 | 431 | Production of IL-6 | L-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | meningus, and Lyme Disease.  A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|         |     |                    | induced lgE production and increases<br>lgA production (lgA plays a role in<br>mucosal immunity). IL-6 induces<br>cytotoxic T cells. Deregulated                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| inisked to response as a sanoughy on the cells sanoughy on the cell in the cel |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| expression of L chris been inked of audoinnume disease, plasma-yonnas, mychomas, and eduvoisies mychomas, and eduvoisies propertion in for immunomedulatory and differentiation factor proteins produced by a large variety of cells where the expression level is smongly regulated by cytokines, growth factors, and humburness are well known in the art and may be used or routinely modified to assess the ability of polypepides of the minitive of polypepides of the minimum outdulation and differentiation and modulater T cell polification and function. Exemplar assess that test for immunomodulation proteins evaluate the production of cytokiars, such as IL-6, and the stimulation and undergonist of Cell profification and functional activities. Such assessive that may be used or routinely modified to rest immunomodulation exertity of polypepides of the invention polypepides of the invention polypepides of the invention produced assessive that may be used or routinely modified to rest immunomodulation exertity of polypepides of the invention includes assessy that may be used or routinely modified to rest immunomodulation; polypepides of the invention include assessy that may be used or nothinely modified to rest immunomodulation; and assessive that may a practical approach.  I "Amphoeyers a practical approach" (Citchdung auflowies and agonise or unagonise or the invention) include assessy data and a promedial approach, and ap | autoirmunue disease, plastranopums, methorinas and ethonic myelomas are version level is atomly regulated by cytokines, growth foreors, and numenos are version from the strand may be used to continuely motified to assess the hilly of polypedies of the myelomic |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| indications include benign indications include benign many cuence. Other prefetred and pre- morphistic conditions, such as for miderations include merrin, puncy toppata, Prefetred indications include merrin, puncy toppata, bredgen's indications include merrin, furname yoperal, knothopita, such mythorian, admitted, AIDS, grantiformious disease, inflammatory purports, and include merrin, muturophila, postrisis, suppression organs and issues, hamophilia, muturophila, postrisis, suppression organs and issues, hamophilia, muturophila, protraits, suppression organs in includion is bransplanted organs in includion is bransplanted organs is infection (e.g., an indication is readership below under "Infections Disease").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | allegy, seltma, and rhimits. Additional highly preferred indications include definitions in the profession of the profes |
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| of each of vitable the contents of each of vitable are herein as each of vitable are herein is entirely. Human dendritic colds that may be used coording to these assays may be isolated colds in the entirely of the cold of the colds of the respective of the respective of the respective of the colds of th | Assays for the activation of transcription through the Signal Transchuers and Activators of Transcription (STAT6) response femeral in immune cells (sach as in heamen Hort, ransc cell line) are well-known in the art and may be used or remitted you forly top why peptides of the investion (rebuiling authories and investion) to regulate STAT6 investion) to regulate STAT6 the investion for investigation for the investigation feature and the convession of multiple genes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Antivation of<br>transcription through<br>STAT6 response<br>defenced in immune<br>cells (such as mast<br>cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 431                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HBJLC01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 27                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                                                                                  | through the Sey for transcription through the STA for seponse cherron than the may be used or rouninely than the sey of t | Inpus erythermatosis, multiple des Er henumotid arthritis, systemic lipus erythermatosis, multiple described below), and immunodeficieteite (e.g., si described below). Proferred immunodeficieteite erse the error blustic diseases; (e.g., lettkernia, lymphoma, membrana, and era steerabel below under "Hyporproliferative brokers"). Preferred indexinosis and cancer; such diseases; (e.g., lettkernia, lymphoma, and cancer; such diseases). Proferred indexinosis include neoplesars and cancer; such and prostact, by preferred indexinosis include benign escappageal, storample, berginglist, practicated indications include benign end pre- tendigistic conditions, such as, for the proferred indications include benign end pre- tendigistic conditions, such as, for the problems, proferred and remanopotical disorders such pre- tendigistic conditions, such as, for the problems, and pre- tendigistic conditions, such as, for the problems of the proble |
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| 27 | HBJLC01 | 431 | Production of RANTES<br>in endothelial cells<br>(such as human<br>umbilical vein | mast cells.  RANYES FMAT. Assays for immunormodulatory proteins that induce chemotaxis of T cells, monocytes, and cosinophils are well                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| known in the art and may be used or<br>routinely modified to assess the | ability of polypeptides of the | agonists or antagonists of the | invention) to mediate | immunomodulation, induce | chemotaxis, and/or mediate humoral | or cell-mediated immunity. | Exemplary assays that test for | immunomodulatory proteins evaluate | the production of cytokines, such as | RANTES, and the induction of | chemotactic responses in immune | cells. Such assays that may be used | or routinely modified to test | immunomodulatory activity of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Miraglia et | al., J Biomolecular Screening 4:193- | 204 (1999); Rowland et al., | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000): Cocchi et | al., Science 270(5243):1811-1815 | (1995); and Robinson et al., Clin Exp | Immunol 101(3):398-407 (1995), the | contents of each of which are herein | incorporated by reference in its | entirety. Endothelial cells that may | be used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary endothelial | cells that may be used according to | these assays include human umbilical | vein endothelial cells (HUVEC), |
|-------------------------------------------------------------------------|--------------------------------|--------------------------------|-----------------------|--------------------------|------------------------------------|----------------------------|--------------------------------|------------------------------------|--------------------------------------|------------------------------|---------------------------------|-------------------------------------|-------------------------------|------------------------------|-------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-----------------------------|-------------------------------------|-------------------------------------|----------------------------------|---------------------------------------|------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------------|-------------------------------------|--------------------------------------|---------------------------------|
| endothelial cells (HUVEC))                                              |                                |                                |                       |                          |                                    |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      | _                               |
|                                                                         |                                |                                |                       |                          |                                    |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      |                                 |

| HBNAW17 432 |
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|    |         |     |                   | according to these assays include the | lymphoma, and/or as described         |
|----|---------|-----|-------------------|---------------------------------------|---------------------------------------|
|    |         |     |                   | CTLL cell line, which is an IL-2      | below under "Hyperproliferative       |
|    |         |     |                   | dependent suspension culture of T     | Disorders"). Additionally, highly     |
|    |         |     |                   | cells with cytotoxic activity.        | preferred indications include         |
|    |         |     |                   |                                       | neoplasms and cancers, such as, for   |
|    |         |     |                   |                                       | example, leukemia, lymphoma,          |
|    |         |     |                   |                                       | melanoma, glioma (e.g., malignant     |
|    |         |     |                   |                                       | glioma), solid tumors, and prostate,  |
|    |         |     |                   |                                       | breast, lung, colon, pancreatic,      |
|    |         |     |                   |                                       | esophageal, stomach, brain, liver and |
|    |         |     |                   |                                       | urinary cancer. Other preferred       |
|    |         |     |                   |                                       | indications include benign            |
|    |         |     |                   |                                       | dysproliferative disorders and pre-   |
|    |         |     |                   |                                       | neoplastic conditions, such as, for   |
|    |         |     |                   |                                       | example, hyperplasia, metaplasia,     |
|    |         |     |                   |                                       | and/or dysplasia. Preferred           |
|    |         |     |                   |                                       | indications include anemia,           |
|    |         |     |                   |                                       | pancytopenia, leukopenia,             |
|    |         |     |                   |                                       | thrombocytopenia, Hodgkin's           |
|    |         |     |                   |                                       | disease, acute lymphocytic anemia     |
|    |         |     |                   |                                       | (ALL), plasmacytomas, multiple        |
|    |         |     |                   |                                       | myeloma, Burkitt's lymphoma,          |
|    |         |     |                   |                                       | arthritis, AIDS, granulomatous        |
|    |         |     |                   |                                       | disease, inflammatory bowel disease,  |
|    |         |     |                   |                                       | neutropenia, neutrophilia, psoriasis, |
|    |         |     |                   |                                       | suppression of immune reactions to    |
|    |         |     |                   |                                       | transplanted organs and tissues,      |
|    |         |     |                   |                                       | hemophilia, hypercoagulation,         |
|    |         |     |                   |                                       | diabetes mellitus, endocarditis,      |
|    |         |     |                   |                                       | meningitis, Lyme Disease, cardiac     |
|    |         |     |                   |                                       | reperfusion injury, and asthma and    |
|    |         |     |                   |                                       | allergy. An additional preferred      |
|    |         |     |                   |                                       | indication is infection (e.g., an     |
|    |         |     |                   |                                       | infectious disease as described below |
|    |         |     |                   |                                       | under "Infectious Disease").          |
| ę  | HBNAW17 | 432 | Insulin Secretion | Assays for measuring secretion of     | A highly preferred indication is      |
| 07 |         |     |                   | Insulin are well-known in the art and | diabetes memus. An auditorial         |

| highly preferred indication is a complication associated with diabetes (e.g., diabetto retinopathy, diabetic replinopathy, kidney disease (e.g., renal failure, nephropathy      | and/or other diseases and disorders as<br>described in the "Renal Disorders"<br>section below), diabetic neuropathy,<br>nerve disease and nerve damage | (e.g., the to diabetic neuropathy),<br>blood vessel blockage, heart disease,<br>stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel<br>blockage), seizures, mental    | contlision, drowaness, nonkeduc<br>hyperglycennic-hyperosmolar coma,<br>cardiovascular disease (e.g., heart<br>disease, attenoseleroiss,<br>microvascular disease, hypertension,<br>stroke, and other diseases and | disorders as described in the declarity as described in the below), dyslipidemia, endocribe disorders (a described in the "Endocribe Disorders" section below), neuropathy, vision impariment (e.g., diabetal erritopathy.                                    | wound beling, and infection (e.g., wound bealing, and infection (e.g., activation sides and disorders is described in the "infections described in the "infections of the uniony text and skin), carpal mane syndrome and Depuyters is contracture). An additional and/or complications associated with and/or complications associated with                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| may be used or routinely modified to assess the ability of polypeptides of the invention (including authodies and agonists or antagonists of the invention) to stimulate insulin | secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta                | cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test | for stimulation of installi secretion (from pancreatic cells) by polypoptides of the invention (including antibodies and agonists or anagonists of the invention) include assays disclosed in: Shimiza, H., et     | all, Fatoor 1, 4(7)251-9 (2000);<br>Salaparek, AM, et al., Mol<br>Endoerinol, 13(8):1305-17 (1999);<br>Filipsson, K., et al., Ann N Y Acad<br>Sci, 865-441-4 (1998; Olson, L.K.,<br>et al., J Biol Chem, 271(28):16544-<br>52 (1996); and, Miraglia S et al., | organia on nonmediate accounts,<br>41(93-20t (1999), the contents of<br>and of which is herein incorporated<br>by reference in its entirely.<br>Percentice of the ann my be task<br>according to these assays are publicly<br>andror may be routinely the ATCC**)<br>andror may be routinely the ATCC**)<br>andror may be routinely agreement.<br>Exemplary pure accounts cells that may<br>be used according to these assays. |
|                                                                                                                                                                                  |                                                                                                                                                        |                                                                                                                                                                                          |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                  |                                                                                                                                                        |                                                                                                                                                                                          |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                  |                                                                                                                                                        |                                                                                                                                                                                          |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                |

| include HITTISTS Cells. HITTIST are operated, Additional cell time an address optidebil cell line indecations include veight loss or established from Syrian bimaser isle alternatively, weight gain. Additional cells transformed with SV40. These highly preferred indications are cells cransformed with SV40. These highly preferred indications are indications from Syrian bimases. The inguly preferred indications are cells excrete insulin, which is calls secrete insulin, which is and approved by someostatin or and suppressed by someostatin or glucocationide. ATITE Refs. Lord and Astrocht. Biochem.  1. 219: 547-551; Samere et al. Proc. | Regulation of Assays for the regulation of transcription through the PIPCK promoter in promoter we well-known in the and may be transcription through the PIPCK promoter in produce we well-known in the and may be transcription through the PIPCK promoter in an angionists of the irrecultural produces and described in the "Renal Disouters" produce rounding the PIPCK promoter that the produces of the irrecultural produces and increase and described in the "Renal Disouters" produce rounding the PIPCK promoter that the produces and increase and described in the "Renal Disouters" produce or necessary of the irrecultural produces of the produces of the irrecultural produces of the ir |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 433 Regulation of transacrition though the PEPCK promoter hepatocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 29 HCE2P54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| Ochimed et al. Dibbers «90(1989).  90 (2000), and Yeagre et al. J 1860 (Chen 275(2));1784 L 1720 (2000), the controls of each of which is herein incorporated by effective in its entirely. Hamology to eith et al. Dibbers assys are publicly withhelf of eg., through its ATCCP3 undro may be used according to these sassys include hardon may be used according to these sassys include Hille cells, with contain a tyosine. Hille cells, with contain a tyosine mainto transferase that is include with glucosorticoids, insulin, or cAMP derivatives. |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                       |                                       | blood disorders (e.g., as described   |
|----|---------|-----|-----------------------|---------------------------------------|---------------------------------------|
|    |         |     |                       |                                       | below under "Immune Activity".        |
|    |         |     |                       |                                       | "Cardiovascular Disorders", and/or    |
|    |         |     |                       |                                       | "Blood-Related Disorders"), immune    |
|    |         |     |                       |                                       | disorders (e.g., as described below   |
|    |         |     |                       |                                       | under "Immune Activity"), infection   |
|    |         |     |                       |                                       | (e.g., an infectious disease and/or   |
|    |         |     |                       |                                       | disorder as described below under     |
|    |         |     |                       |                                       | "Infectious Disease"), endocrine      |
|    |         |     |                       |                                       | disorders (e.g., as described below   |
|    |         |     |                       |                                       | under "Endocrine Disorders"), and     |
|    |         |     |                       |                                       | neural disorders (e.g., as described  |
|    |         |     |                       |                                       | below under "Neural Activity and      |
|    |         |     |                       |                                       | Neurological Diseases").              |
|    |         |     |                       |                                       | Additional preferred indications      |
|    |         |     |                       |                                       | include neoplastic diseases (e.g., as |
|    |         |     |                       |                                       | described below under                 |
|    |         |     |                       |                                       | "Hyperproliferative Disorders").      |
|    |         |     |                       |                                       | Preferred indications include         |
|    |         |     |                       |                                       | neoplasms and cancers, such as,       |
|    |         |     |                       |                                       | leukemia, lymphoma, prostate,         |
|    |         |     |                       |                                       | breast, lung, colon, pancreatic,      |
|    |         |     |                       |                                       | esophageal, stomach, brain, and       |
|    |         |     |                       |                                       | urinary cancer. A highly preferred    |
|    |         |     |                       |                                       | indication is liver cancer. Other     |
|    |         |     |                       |                                       | preferred indications include benign  |
|    |         |     |                       |                                       | dysproliferative disorders and pre-   |
|    |         |     |                       |                                       | neoplastic conditions, such as, for   |
|    |         |     |                       |                                       | example, hyperplasia, metaplasia,     |
|    |         |     |                       |                                       | and/or dysplasia.                     |
|    | HCE2F54 | 433 | Activation of         | Assays for the activation of          | Preferred embodiments of the          |
| 29 |         |     | transcription through | transcription through the NFKB        | invention include using polypeptides  |
|    |         |     | NFKB response         | response element are well-known in    | of the invention (or antibodies,      |
|    |         |     | element in epithelial | the art and may be used or routinely  | agonists, or antagonists thereof) in  |
|    |         |     | cells (such as HELA   | modified to assess the ability of     | detection, diagnosis, prevention,     |
|    |         |     | cells).               | polypeptides of the invention         | and/or treatment of Cancer, Wound     |
|    |         |     |                       | (including antibodies and agonists or | Healing, and Inflamation. Highly      |

| erribed and and hung, hung, by ty                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                             |
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| es (e.g., sa de se (e.g., sa d |                                                                                                                                                             |
| preferred inflatations include to repopulate diseases (e.g., as described between water Highly preferred inflations and "Highly preferred inflations include incoplasms and curents, such as, for example, order, prostate, breast, lung, melanoma, and prostate, breast, lung, conden, paracraft, essphagati, somach, brain, liver and urinary amount, of the preferred inflations, include braing hysporlicative diseases, such as, for example, hyperplasa, urangilasi, and/or dysplasia. Preferred inflations include include include include include include include include includes include includes inflammation disorders.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                             |
| regulate VFKB transcription factors and managemists of the invention) to regulate Capression of the invention included the capression element activity of the capression of the invention included and capression elements of the invention included at al., Choogene, 18(1):2213-2325 at 1.029; Peter Art. at., Intl. Badnin Biol., 76(11):1441-1453 (2000).  Biol., 1549: Beach, 26(1988; Valle Biol., Prop. Natl. Acad. Sci. 1092).  Cultum and Malin, Methods in al., Pro Natl Acad. Sci. 1092; Acad. Prop. Acad. | REPLA CELL INE.  REPORTER ASSAY: CONSTRUCT CONTAINS  regulatory and coding sequence of  squatence synthetase, the first specific  enzyme in the cholesterol |
| antage regular antage regular antage regular antage regular for the form on the form of th |                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Inhibition of squalene<br>synthetase gene<br>transcription.                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 433                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCE2F54 4                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 29                                                                                                                                                          |

| biosynthetic pathway. See Jiang, et al., 1 Biol. Chem. 26812818. 128241(959), the contents of which we have herein incoproacid by reference in its entirety. Cells were treated in the SID spectrations, and SLAP activity was measured alter 72 hours activity was measured alter 72 hours continuous et al. Science. 1995. See Knowless et al., Science. 2095-497-9 (1980), the contents of reference in its entirety. | increases or decreases) of vitability and aways for the regulation (i.e., increases or decreases) of vitability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polyperpidies of the invention (including antibodies) and invention (including antibodies) and invention to regulate vitability and possible and any or explaint vitability and possible and or explaint vitability and cell lines. For example, the cell lines for example to the measure the rumber of vitable cells in measure the rumber of vitable cells in measure the rumber of vitable cells in example is ginate the presence of metabolically active cell line. It is a mouse preadqueyte cell line. It is a dispession of the cell selected of cells selected or cells were cell excelpered to an adioses-like state differentiated to an adioses-like state |
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|                                                                                                                                                                                                                                                                                                                                                                                                                          | information of pre- adpose celts (such as 3T3-L1 celts)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                          | Ş                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                          | HCE2F54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                          | 29                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| before being used in the screen. See Green H and Meuth M., Cell 3: 127-137 (1974), which is berein incorporated by reference in its entirety. | This importes uses measures activation or the NEBB signaling public with the NEBB signaling public with the NEBB signaling public will be submitted or inhibition of the new of the new or inhibition of the new of the new or inhibition of the new of the |
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|                                                                                                                                               | Activation or inhibition Activation or inhibition NFKB response Activation in immune Calls (such as basophils).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                               | 493                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                               | HCE2F54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                               | 53                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| are herein incorporated by reference with SID supermetants or controls for its entirely. Cells were perfected with SID supermetants or controls for TIP 4-s8 hours, and then 10 ng/mL of TIP 4-s8 hours, and of 10 simulate the backers of the perfect of the supermetant of the superm | This susquest as HIKB tresponse clement (which will bind HKB transcription factors) linked to a framewription factors) linked to a proporter gene to measure MKB modiated transcription in the human moneyue cell line U937. MREB is upregulated by cytokines and other immunosmodulatory geness, developen and consequent of the ARB tement activation of MKB in moneyers can piece and the minimum activation of MKB in moneyers can piny a toole in immune responses. Cent piny a toole in immune responses.  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of transcription through NeRG response clement in immediate cells (such as internal monocyte cell line).                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 433                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCE2F54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 29                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| modified to est NKB-response<br>modified to est NKB-response<br>that may be used to Polypeptides of<br>the invention (including ambiodies and<br>the invention (including ambiodies<br>and agonists or mangensis of the<br>invention) include assays (acle off<br>invention) include assays (acle off<br>invention) include assays (acle off<br>the mangeness). As a second of the<br>collection and Mahn, Methods in<br>Hendrom et al., Proc Natl Acad Sci<br>Hendrom et al., Proc Natl<br>Acad Sci Sci<br>Hendrom et al., Proc Natl<br>Acad Sci<br>Hendrom et al., Proc | de, as describe blow). An additional highly preferred indication infections (e.g., AIDS, and or an infections disease as described below). The indication disease as described below methods of disease (e.g., malmonn, preferred indications include or supering diseases (e.g., malmonn, lenkemin, lymphonn, under or secretive blow under described below under described below in directions, lenkemin, lymphonn, under describent how conferences and encores, such moophasms and encores, such moophasms and encores, such encorement of contributions in the conference of the disease of the conference of the confere |
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| or neces seasons include the USF7 cell fine, which is include the USF7 cell fine, which is like a limit of the Cell fine, which is like an include the USF8 or in USF4 from malignant cells obtained from the pleural effision of a patient with histocytic lymphoma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | reductions as and relucte entirus, pancytopenia, letkopenia, neturopenia, ne |

| regulatory construct contains regulatory and coding sequence of squatere synthesise, the first specific control in the Cas in thus me person control in the | increases or decreases) of violating masses for the regulation (i.e., increases or decreases) of violating and proliferation of cells in vitro are and motification of cells in vitro are used or routinely modified to assess the builty of polyperdies of the invention (including antibodies and agreement of the properties of the invention) to regulate viability and programs or antiposition of the invention) to regulate viability and programs of a priminescent Cell intensive and cell lines. For example, the cell lines for example, the cell lines for example, the constant for humane or viable cells in massure the number of viable cells in culture based on quantitation of the pressure of metabolically stative pressure of metabolically stative cell line. It is an mouse preadpocyte cell line, It is an mouse |
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| Imbilition of squalere<br>synthetise gare<br>transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | olification of pre- adjones cells (such as 373-L1 cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 434                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 464                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| HCE3G69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HCE3G69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|    |          |     |                                      | orintions as sharin of \$13 in<br>fluorbias celes developed through<br>condarisabilitation Cells were<br>deficeratisated to an adjosse-like state<br>before being used in the screen, See<br>the Cener II and Menth M., Cell § 127-<br>135 (1974), which is been<br>135 (1974), which is been<br>empropriated by reference in its<br>entirety.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----|----------|-----|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 30 | HC13 G69 | 434 | secución from pancreatic beta cells. | insulin acwass for measuring secretion of insulin are well-known in the art and measures between vell-known in the art and measures the ability of polyperpides of the invention floating ambidies and agentise or matagniss of the invention to stimulate insulin invention) to stimulate insulin secretion for example, FMAT insulin secretion from paractic beat accretion from paractic beat accretion from paractic beat of the insulin secretion from paractic beat of the insuling and real minim antibodists. Insulin secretion from paractic of set to predict by glucose and also by certain proteins peptides, and also by certain proteins peptides, and also by certain proteins peptides, and disheres. Exemplity seasys that may for simulation of insulin secretion from patersate of cells by polypedides of the invention of insulin secretion from paractic occlets by polypedides of the invention include an amagoniss of the invention include an amagoniss of the invention include an anagonis of the invention include an anagonis and an Endevintion (1997); Kim, K. H., Am J Physiol, L. M., al. Endevintioning S. et al., 419(1997); Kim, K. H., 18(9); S. et al., HERS Lett, A. T(2); 2737. | A highly preferred indication is diahotes mellins.  A highly preferred indication is a complication associated with foreign diahotes (e.g. diahotes) (e.g. dia |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly preferred indication is<br>diabetes mellins.  A highly preferred indication<br>is a complication superior preferred indication<br>is a complication associated with<br>diabetes (e.g., diabetic retinopathy,<br>diabetic incaptropathy kitney disease<br>(e.g., renal failure, nephropathy<br>and/or other diseases and diseaters as<br>described in the 'Renal Disaoders'<br>exceptible of the disease and nerve damage<br>of a due to disease and nerve damage<br>blood vessa blockege, heart disease.                                                                 |
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| DS, et al., "Th-2 cytokines in allegic desease" by Melb His 56 (4) 256-588 (2000), and Golm, et al., "Th-6 pher type 2 cell-directed therapy for ashma" Pharmacology & Therapoulose, 88 187-196 (2000), the contents of each of whith are breach or whith any be used according to these assets the analysis of the contents o | seasys for measuring secretion of insain are well-known in te art and may be used or nontheir modifierd to assess the ability of holyrepides of the invention lost anagonises on the invention lost attaining analysis of the invention lost attaining analysis of the invention lost attaining analysis of the invention lost attaining analysis and analysis are attained by IMAAT assign anti-test attaining accretion from pracractic bena testing accretion from pracractic bena classification of the proposal of the properties and also by certain proteins/peptides, and |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Simulation of insulin secretion from pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 43.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCESF43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | £                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

|    |         |     |                       | dispendation is a key component in      | stroke inmotence (e.g. due to          |
|----|---------|-----|-----------------------|-----------------------------------------|----------------------------------------|
|    |         |     |                       | diabetes Exemplary assays that may      | diahetic neuronathy or blood vessel    |
|    |         |     |                       | be used or routinely modified to test   | blockage), seizures, mental            |
|    |         |     |                       | for stimulation of insulin secretion    | confusion, drowsiness, nonketotic      |
|    |         |     |                       | (from pancreatic cells) by              | hyperglycemic-hyperosmolar coma,       |
|    |         |     |                       | polypeptides of the invention           | cardiovascular disease (e.g., heart    |
|    |         |     |                       | (including antibodies and agonists or   | disease, atherosclerosis,              |
|    |         |     |                       | antagonists of the invention) include   | microvascular disease, hypertension,   |
|    |         |     |                       | assays disclosed in: Ahren, B., et al., | stroke, and other diseases and         |
|    |         |     |                       | Am J Physiol, 277(4 Pt 2):R959-66       | disorders as described in the          |
|    |         |     |                       | (1999); Li, M., et al., Endocrinology,  | "Cardiovascular Disorders" section     |
|    |         |     |                       | 138(9):3735-40 (1997); Kim, K.H.,       | below), dyslipidemia, endocrine        |
|    |         |     |                       | et al., FEBS Lett, 377(2):237-9         | disorders (as described in the         |
|    |         |     |                       | (1995); and, Miraglia S et. al.,        | "Endocrine Disorders" section          |
|    |         |     |                       | Journal of Biomolecular Screening,      | below), neuropathy, vision             |
|    |         |     |                       | 4:193-204 (1999), the contents of       | impairment (e.g., diabetic retinopathy |
|    |         |     |                       | each of which is herein incorporated    | and blindness), ulcers and impaired    |
|    |         |     |                       | by reference in its entirety.           | wound healing, and infection (e.g.,    |
|    |         |     |                       | Pancreatic cells that may be used       | infectious diseases and disorders as   |
|    |         |     |                       | according to these assays are publicly  | described in the "Infectious           |
|    |         |     |                       | available (e.g., through the ATCCTM)    | Diseases" section below, especially    |
|    |         |     |                       | and/or may be routinely generated.      | of the urinary tract and skin), carpal |
|    |         |     |                       | Exemplary pancreatic cells that may     | tunnel syndrome and Dupuytren's        |
|    |         |     |                       | be used according to these assays       | contracture). An additional            |
|    |         |     |                       | include rat INS-1 cells. INS-1 cells    | highly preferred indication is obesity |
|    |         |     |                       | are a semi-adherent cell line           | and/or complications associated with   |
|    |         |     |                       | established from cells isolated from    | obesity. Additional highly preferred   |
|    |         |     |                       | an X-ray induced rat transplantable     | indications include weight loss or     |
|    |         |     |                       | insulinoma. These cells retain          | alternatively, weight gain.            |
|    |         |     |                       | characteristics typical of native       | Aditional highly preferred             |
|    |         |     |                       | pancreatic beta cells including         | indications are complications          |
|    |         |     |                       | glucose inducible insulin secretion.    | associated with insulin resistance.    |
|    |         |     |                       | References: Asfari et al.               |                                        |
|    |         |     |                       | Endocrinology 1992 130:167.             |                                        |
|    | HCEFB80 | 436 | Activation of         | Assays for the activation of            | Highly preferred indications           |
| 32 |         |     | transcription through | transcription through the Gamma         | include neoplastic diseases (e.g.,     |
|    |         |     | GAS response element  | Interferon Activation Site (GAS)        | leukemia, lymphoma, and/or as          |

| described below under "Hyperproliferative Disorders"). Highly preferred indications include                     | neoplasms and cancers, such as, for<br>example, leukemia, lymphoma (e.g.,<br>T cell lymphoma, Burkit's<br>lymphoma, non-Hodgkins<br>lymphoma Hodskin's disease)                    | y-in-port, rotegin or integral, img, colon, pancrettic, esophageal, storach, brain, liver and unitary sancer. Other preferred indications include benign dysproliferative         | disorders and pre-trooplastic<br>conditions, such as, for example,<br>hyperplasia, metaplasia, and/or<br>dysplasia. Preferred indications<br>include autoimnume diseases (e.g.,<br>rheumatoid arthrifis, systemic lupus | experimentos, amilios sciencis and control months seems in and control                                                                                                                      | disorders. Highly preferred intensationary administrations included blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders, and "Ordinovascular Disorders," and infection (e.g., viral infections, underenlosis, infections associated with chronic granhlormious diseases and granhlormious diseases and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| response element are well-known in<br>the art and may be used or routinely<br>modified to assess the ability of | polypeptaces of the airvention<br>(including antibodies and agonists or<br>antagonists of the invention) to<br>regulate STAT transcription factors<br>and modulate sene expression | involved in a vide variety of cell<br>functions. Exemplary assays for<br>transcription through the GAS<br>response element that may be used or<br>routinely modified to test GAS- | response element activity of polypeptides of the invention (including antibodies and agonisis or antagonisis of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998), Cullen and               | 216:362-368 (1992); Henthem et al.,<br>Phere Natl Acad Set USA 85:6342-<br>6346 (1988); Matthemm et al.,<br>Blood 93(6):1980-1991 (1999); and<br>Blood 93(6):1980-1991 (1999); and<br>Blood 1960-1980-1991 (1999); and<br>155(10):4582-4587 (1995), the<br>contents of each of which are beterin<br>inconversard har effective in its<br>inconversard har effe | entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., newplay available (e.g., newplay available (e.g., newplay available (e.g., newplay for the public of the |
| in immune cells (such as T-cells).                                                                              |                                                                                                                                                                                    |                                                                                                                                                                                   |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                 |                                                                                                                                                                                    |                                                                                                                                                                                   |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|    |         |     |                  | nolyneptides of the invention          | cardiovascular disease (e.g. heart     |
|----|---------|-----|------------------|----------------------------------------|----------------------------------------|
|    |         |     |                  | (including antibodies and agonists or  | disease, atherosclerosis,              |
|    |         |     |                  | antagonists of the invention) include  | microvascular disease, hypertension,   |
|    |         |     |                  | assays disclosed in: Shimizu, H., et   | stroke, and other diseases and         |
|    |         |     |                  | al., Endocr J, 47(3):261-9 (2000);     | disorders as described in the          |
|    |         |     |                  | Salapatek, A.M., et al., Mol           | "Cardiovascular Disorders" section     |
|    |         |     |                  | Endocrinol, 13(8):1305-17 (1999);      | below), dyslipidemia, endocrine        |
|    |         |     |                  | Filipsson, K., et al., Ann N Y Acad    | disorders (as described in the         |
|    |         |     |                  | Sci, 865:441-4 (1998); Olson, L.K.,    | "Endocrine Disorders" section          |
|    |         |     |                  | et al., J Biol Chem, 271(28):16544-    | below), neuropathy, vision             |
|    |         |     |                  | 52 (1996); and, Miraglia S et. al.,    | impairment (e.g., diabetic retinopathy |
|    |         |     |                  | Journal of Biomolecular Screening,     | and blindness), ulcers and impaired    |
|    |         |     |                  | 4:193-204 (1999), the contents of      | wound healing, and infection (e.g.,    |
|    |         |     |                  | each of which is herein incorporated   | infectious diseases and disorders as   |
|    |         |     |                  | by reference in its entirety.          | described in the "Infectious           |
|    |         |     |                  | Pancreatic cells that may be used      | Diseases" section below, especially    |
|    |         |     |                  | according to these assays are publicly | of the urinary tract and skin), carpal |
|    |         |     |                  | available (e.g., through the ATCCTM)   | tunnel syndrome and Dupuytren's        |
|    |         |     |                  | and/or may be routinely generated.     | contracture). An additional            |
|    |         |     |                  | Exemplary pancreatic cells that may    | highly preferred indication is obesity |
|    |         |     |                  | be used according to these assays      | and/or complications associated with   |
|    |         |     |                  | include HITT15 Cells. HITT15 are       | obesity. Additional highly preferred   |
|    |         |     |                  | an adherent epithelial cell line       | indications include weight loss or     |
|    |         |     |                  | established from Syrian hamster islet  | alternatively, weight gain. Additional |
|    |         |     |                  | cells transformed with SV40. These     | highly preferred indications are       |
|    |         |     |                  | cells express glucagon, somatostatin,  | complications associated with insulin  |
|    |         |     |                  | and glucocorticoid receptors. The      | resistance.                            |
|    |         |     |                  | cells secrete insulin, which is        |                                        |
|    |         |     |                  | stimulated by glucose and glucagon     |                                        |
|    |         |     |                  | and suppressed by somatostatin or      |                                        |
|    |         |     |                  | glucocorticoids. ATTC# CRL-1777        |                                        |
|    |         |     |                  | Refs: Lord and Ashcroft. Biochem.      |                                        |
|    |         |     |                  | J. 219: 547-551; Santerre et al. Proc. |                                        |
|    |         |     |                  | Natl. Acad. Sci. USA 78: 4339-4343,    |                                        |
|    |         |     |                  | 1981.                                  |                                        |
|    | HCENK38 | 437 | Protection from  | Caspase Apoptosis Rescue. Assays       | A highly preferred embodiment of       |
| 33 |         |     | Endothelial Cell | for caspase apoptosis rescue are well  | the invention includes a method for    |

| Apoptosis, known in the art and may be used or nutrinely modified to assess the ability of the polyspeptides of the intervent of including antibodies and against or antigorities of the intervent of including antibodies and against or antigorities of the properties of the invention (including antibodies and apoptosis. Exemplary assess por coapses apoptosis that may be used or notitietly modified to test caspises apoptosis that may be used or notitietly modified to test caspises apoptosis seasue of polyspetides of the invention fordienting antibodies and agoniss or antigonists of the invention fordienting antibodies and agoniss or antigonists of the invention produce the usessor and agoniss or antigonists of the invention produce the usessor and agoniss or antigorists of the invention produce the usessor and agoniss or antigorism of the agonism of the assays and the bown and the agonism of the a | stimulating endothelial cell growth. | An alternative highly preferred  | embodiment of the invention        | includes a method for inhibiting    | endothelial cell growth. A highly | preferred embodiment of the   | invention includes a method for | stimulating endothelial cell | proliferation. An alternative highly | preferred embodiment of the        | invention includes a method for     | inhibiting endothelial cell         | proliferation. A highly preferred  | embodiment of the invention   | includes a method for stimulating     | endothelial cell growth. An        | alternative highly preferred         | embodiment of the invention    | includes a method for inhibiting | endothelial cell growth. A highly    | preferred embodiment of the      | invention includes a method for      | stimulating apoptosis of endothelial  | cells. An alternative highly preferred | embodiment of the invention    | includes a method for inhibiting (e.g., | decreasing) apoptosis of endothelial | cells. A highly preferred       | embodiment of the invention     | includes a method for stimulating  | angiogenisis. An alternative highly   | preferred embodiment of the           | invention includes a method for      | inhibiting angiogenesis. A highly | preferred embodiment of the | invention includes a method for | reducing cardiac hypertrophy. An |
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| Apoptosis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | known in the art and may be used or  | routinely modified to assess the | ability of the polypeptides of the | invention (including antibodies and | agonists or antagonists of the    | invention) to inhibit caspase | protease-mediated apoptosis.    | Exemplary assays for caspase | apoptosis that may be used or        | routinely modified to test caspase | apoptosis rescue of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include the assays | disclosed in Romeo et al., Cardiovasc | Res 45(3): 788-794 (2000); Messmer | et al., Br J Pharmacol 127(7): 1633- | 1640 (1999); and J Atheroscler | Thromb 3(2): 75-80 (1996); the   | contents of each of which are herein | incorporated by reference in its | entirety. Endothelial cells that may | be used according to these assays are | publicly available (e.g., through      | commercial sources). Exemplary | endothelial cells that may be used      | according to these assays include    | bovine aortic endothelial cells | (bAEC), which are an example of | endothelial cells which line blood | vessels and are involved in functions | that include, but are not limited to, | angiogenesis, vascular permeability, | vascular tone, and immune cell    | extravasation.              |                                 |                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Apoptosis.                           |                                  |                                    |                                     |                                   |                               |                                 |                              |                                      |                                    |                                     |                                     |                                    |                               |                                       |                                    |                                      |                                |                                  |                                      |                                  |                                      |                                       |                                        |                                |                                         |                                      |                                 |                                 |                                    |                                       |                                       |                                      |                                   |                             |                                 |                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                      |                                  |                                    |                                     |                                   |                               |                                 |                              |                                      |                                    |                                     |                                     |                                    |                               |                                       |                                    |                                      |                                |                                  |                                      |                                  |                                      |                                       |                                        |                                |                                         |                                      |                                 |                                 |                                    |                                       |                                       |                                      |                                   |                             |                                 | _                                |

|   | survoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's surcoma, hermagiona (capillary and exervenous, by domist runves to loperiosessis and carbonals, polymerations to loperiosessis and polymerations in the health of the polymeration of the health of the polymeration of the health of |
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|   | sarooma, and retutal autosocies. Highly preferred indeations indeations indeations indeations indeations. Kapooff's sarooma, hemangioma Kapooff's sarooma, hemangioma (ceptilizaro de ceptilizaro  de ceptili |
|   | Highly preterred indications inch in reophasms and cancer; such as Kapoel's serooma, hermagoma (capillary and everyone); glomus improve plannievesia hocillary improve plannievesia hocillary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|   | neoplasms and cancer, such as, Kapost's strooma, hemangoma (capillary and cavernous), glomus immer elebaricoses hocillary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|   | Kaposi's sarcoma, hemangioma<br>(capillary and cavernous), giornus<br>transve releaniscesse becellere                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|   | (capillary and cavernous), glomus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|   | thmore telemeiscrasia hacillary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   | common of the co |
|   | angiomatosis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|   | hemangioendothelioma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|   | angiosarcoma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|   | haemangiopericytoma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|   | lymphangioma, lymphangiosarcoma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|   | Highly preferred indications also                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|   | include cancers such as, prostate,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | breast, lung, colon, pancreatic,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|   | esophageal, stomach, brain, liver,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | and uninary cancer. Preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|   | indications include benign                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| _ | dysproliferative disorders and pre-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   | neoplastic conditions, such as, for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   | S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|   | and/or dysplasia. Highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|   | preferred indications also include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | arterial disease, such as,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|   | atherosclerosis, hypertension,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|   | coronary artery disease,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|   | inflammatory vasculitides,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|   | Reynaud"s disease and Reynaud"s                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   | phenomenom, aneurysms, restenosis;                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | venous and lymphatic disorders such                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   | as thrombophlebitis, lymphangitis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | and lymphedema; and other vascular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | disorders such as peripheral vascular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|   | disease, and cancer. Highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|   | preferred indications also include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   | trauma such as wounds, burns, and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|   | injured tissue (e.g., vascular injury                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|  | such as, injury resulting from belloon<br>angiophasy, and atherosohherotic<br>lesions), implant frastion, searring, | ischemia erpertitison mjury, rischemia erpertitison mjury, rheumatoid arthritis, cerebrovascular disease, rend diseases such is acute rend fillure, and diseases | Additional ingility preferred indications include stroke, graft registration, dishelve or other registration, dishelve or other registration, dishelve or other registration of strokes, thrombotic and recipiopatilise, thrombotic and recipiopatilise, thrombotic and recipional strokes, was until in hymph arapigomenis, sexual dishelves and resultant dishelves are resultant dishelves and resultant dishelves are resu | Provention of endometriosis and requested confinous Additional highly preferred indications include from the confinous heard disease, cardiac fromus heard disease, cardiac arrest, heart valve disease, and avesular disease. Preferred indications include blood diseases and vascular disease. Preferred indications include blood diseases and variety of the confinous from the confinous minductions include blood diseaders (e.g., as described below under "frammer Activity", "Shook Sedauch "Disouters", and ov "Cardiovascular and confinous minductions and over "Cardiovascular and confinous minductions". "Shook Sedauch "Disouters", and ov "Cardiovascular and confinous | Disorders), Perfectared indications include autoimmune diseases (e.g., inclumanto del misso (e.g., inclumanto del misso (e.g., inclumanto del misso systemic liquis evydemanosis, multiple selectoris ended of misso experimento del consistenti del misso  |
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Crohn's disease), and pain<br>management. | include recoplastic diseases (e.g., efficient, bympotente diseases) (e.g., effection, bympotente, diseases) (e.g., effection, bympotente, and or as described below under an add or as described below under a described below, and or objects, and or objects of the objects of the object of the distinct of immune response, and dinformation and inflammatory financiared inflammatory include blood disorders and inflammatory include blood disorders. |
|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                           | transcription though the Gumma<br>transcription though the Gumma<br>transcription though the Gumma<br>the art and may be used or routinely<br>the art and may be used or routinely<br>the art and may be used or routinely<br>the art and may be used or routinely<br>modified to saxes the ability of<br>polypeptides or the invention) to<br>polypeptides or the invention) to<br>an analysis of the invention) to<br>an analysis of the invention) to<br>an analysis of the invention and<br>functions. Exemplary assays for<br>transcription through the GAS<br>response element that may be used or<br>functions. Exemplary assays for<br>transcription through the GAS<br>response element that may be used or<br>response element that may be used or<br>response element activity of<br>the manner production of the art of the<br>response element activity of<br>the function of the invention include<br>assays disclosed in Berger et al.,<br>Get (1988) Holdis in Enzymen et al.,<br>Proc Nad Acad Sci 15A 85 6342.<br>Proc Nad Acad Sci 15A 85 6342.<br>Blood 34(6) 1980-1991 (1999), and<br>Halm, Methods in Enzymen et al.,<br>Blood 34(6) 1980-1991 (1999), and<br>Halming et al., in mannel<br>incorporated by reference in its<br>incorporated by reference in its<br>incorporated by reference in its<br>incorporated by reference in its<br>incorporated by reference in its<br>that may be used according to these                |
|                                           | Activation of Transaction of Caraction                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                           | 437                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                           | HCENK38                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                           | 33                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|    |         |     |                   | cells that may be used according to<br>these assays include the CTLL cell | Disorders", and/or "Cardiovascular<br>Disorders"), and infection (e.g., viral |
|----|---------|-----|-------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
|    |         |     |                   | line, which is a suspension culture of                                    | infections, tuberculosis, infections                                          |
|    |         |     |                   | IL-2 dependent cytotoxic T cells.                                         | associated with chronic                                                       |
|    |         |     |                   |                                                                           | granulomatosus disease and                                                    |
|    |         |     |                   |                                                                           | malignant osteoporosis, and/or an                                             |
|    |         |     |                   |                                                                           | infectious disease as described below                                         |
|    |         |     |                   |                                                                           | under "Infectious Disease"). An                                               |
|    |         |     |                   |                                                                           | additional preferred indication is                                            |
|    |         |     |                   |                                                                           | idiopathic pulmonary fibrosis.                                                |
|    |         |     |                   |                                                                           | Preferred indications include anemia,                                         |
|    |         |     |                   |                                                                           | pancytopenia, leukopenia,                                                     |
|    |         |     |                   |                                                                           | thrombocytopenia, acute                                                       |
|    |         |     |                   |                                                                           | lymphocytic anemia (ALL),                                                     |
|    |         |     |                   |                                                                           | plasmacytomas, multiple myeloma,                                              |
|    |         |     |                   |                                                                           | arthritis, AIDS, granulomatous                                                |
|    |         |     |                   |                                                                           | discase, inflammatory bowel disease,                                          |
|    |         |     |                   |                                                                           | sepsis, neutropenia, neutrophilia,                                            |
|    |         |     |                   |                                                                           | psoriasis, suppression of immune                                              |
|    |         |     |                   |                                                                           | reactions to transplanted organs and                                          |
|    |         |     |                   |                                                                           | tissues, hemophilia,                                                          |
|    |         |     |                   |                                                                           | hypercoagulation, diabetes mellitus,                                          |
|    |         |     |                   |                                                                           | endocarditis, meningitis, Lyme                                                |
|    |         |     |                   |                                                                           | Disease, and asthma and allergy.                                              |
|    | HCENK38 | 437 | Activation of     | Kinase assay. Kinase assays, for                                          | A highly preferred embodiment of                                              |
| 33 |         |     | Hepatocyte ERK    | example an Elk-1 kinase assay, for                                        | the invention includes a method for                                           |
|    |         |     | Signaling Pathway | ERK signal transduction that regulate                                     | stimulating hepatocyte cell                                                   |
|    |         |     |                   | cell proliferation or differentiation                                     | proliferation. An alternative highly                                          |
|    |         |     |                   | are well known in the art and may be                                      | preferred embodiment of the                                                   |
|    |         |     |                   | used or routinely modified to assess                                      | invention includes a method for                                               |
|    |         |     |                   | the ability of polypeptides of the                                        | inhibiting hepatocyte cell                                                    |
|    |         |     |                   | invention (including antibodies and                                       | proliferation. A highly preferred                                             |
|    |         |     |                   | agonists or antagonists of the                                            | embodiment of the invention                                                   |
|    |         |     |                   | invention) to promote or inhibit cell                                     | includes a method for stimulating                                             |
|    |         |     |                   | proliferation, activation, and                                            | hepatocyte cell differentiation. An                                           |
|    |         |     |                   | differentiation. Exemplary assays for                                     | alternative highly preferred                                                  |
|    |         |     |                   | ERK kinase activity that may be used                                      | embodiment of the invention                                                   |

| or routinely modified to test ERK       | includes a method for inhibiting        |
|-----------------------------------------|-----------------------------------------|
| kinase-induced activity of              | hepatocyte cell differentiation. A      |
| polypeptides of the invention           | highly preferred embodiment of the      |
| (including antibodies and agonists or   | invention includes a method for         |
| antagonists of the invention) include   | activating hepatocyte cells. An         |
| the assays disclosed in Forrer et al.,  | alternative highly preferred            |
| Biol Chem 379(8-9):1101-1110            | embodiment of the invention             |
| (1998); Kyriakis JM, Biochem Soc        | includes a method for inhibiting the    |
| Symp 64:29-48 (1999); Chang and         | activation of and/or inactivating       |
| Karin, Nature 410(6824):37-40           | hepatocyte cells. Highly preferred      |
| (2001); and Cobb MH, Prog Biophys       | indications include disorders of the    |
| Mol Biol 71(3-4):479-500 (1999);        | liver and/or endocrine disorders (e.g., |
| the contents of each of which are       | as described below under "Endocrine     |
| herein incorporated by reference in     | Disorders"). Preferred indications      |
| its entirety. Rat liver hepatoma cells  | include neoplastic diseases (e.g., as   |
| that may be used according to these     | described below under                   |
| assays are publicly available (e.g.,    | "Hyperproliferative Disorders"),        |
| through the ATCCTM). Exemplary          | blood disorders (e.g., as described     |
| rat liver hepatoma cells that may be    | below under "Immune Activity",          |
| used according to these assays          | "Cardiovascular Disorders", and/or      |
| include H4lle cells, which are known    | "Blood-Related Disorders"), immune      |
| to respond to glucocorticoids, insulin, | disorders (e.g., as described below     |
| or cAMP derivatives.                    | under "Immune Activity"), neural        |
|                                         | disorders (e.g., as described below     |
|                                         | under "Neural Activity and              |
|                                         | Neurological Diseases"), and            |
|                                         | infection (e.g., as described below     |
|                                         | under "Infectious Disease").            |
|                                         | A highly preferred indication is        |
|                                         | diabetes mellitus. An additional        |
|                                         | highly preferred indication is a        |
|                                         | complication associated with            |
|                                         | diabetes (e.g., diabetic retinopathy,   |
|                                         | diabetic nephropathy, kidney disease    |
|                                         | (e.g., renal failure, nephropathy       |
|                                         | and/or other diseases and disorders as  |
|                                         | described in the "Renal Disorders"      |

|  | section below), diabetic neuropathy,   |
|--|----------------------------------------|
|  | nerve disease and nerve damage         |
|  | (e.g., due to diabetic neuropathy),    |
|  | blood vessel blockage, heart disease,  |
|  | stroke, impotence (e.g., due to        |
|  | diabetic neuropathy or blood vessel    |
|  | blockage), seizures, mental            |
|  | confusion, drowsiness, nonketotic      |
|  | hyperglycemic-hyperosmolar coma,       |
|  | cardiovascular disease (e.g., heart    |
|  | disease, atherosclerosis,              |
|  | microvascular disease, hypertension,   |
|  | stroke, and other diseases and         |
|  | disorders as described in the          |
|  | "Cardiovascular Disorders" section     |
|  | below), dyslipidemia, endocrine        |
|  | disorders (as described in the         |
|  | "Endocrine Disorders" section          |
|  | below), neuropathy, vision             |
|  | impairment (e.g., diabetic retinopathy |
|  | and blindness), ulcers and impaired    |
|  | wound healing, infection (e.g.,        |
|  | infectious diseases and disorders as   |
|  | described in the "Infectious           |
|  | Diseases" section below, especially    |
|  | of the urinary tract and skin), carpal |
|  | tunnel syndrome and Dupuytren's        |
|  | contracture). An additional highly     |
|  | preferred indication is obesity and/or |
|  | complications associated with          |
|  | obesity. Additional highly preferred   |
|  | indications include weight loss or     |
|  | alternatively, weight gain.            |
|  | Additional highly preferred            |
|  | indications are complications          |
|  | associated with insulin resistance.    |
|  | Additional highly preferred            |

|    |         |     |                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | musculoskeletal systems including musculoskeletal systems including myopathies, muscular dystrophy, myopathies, muscular dystrophy, and/or as described herein, and/or as described herein, Additional lightly preferred factories including his preferred factories including his preferred factories, including his preferred disease, also his preferred disease, dyslipiderin and myopathies, there represents in metabolic disease, dyslipiderin and miscular professers and colon miscular preferred disease, dyslipiderin and elización in hidra front all miscular pradictional highly preferred disease, dyslipiderin and miscular preferred elización sind herein and uning cancer. Such a duranty cancer. Other in, and uning cancer of indications and pre-preferred indications include benign dysprolificative disaculars and pre-ceaming, hypophisia, menghasia, me |
|----|---------|-----|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 46 | HCEWE20 | 438 | Regulation of<br>transcription of Malic<br>Enzyme in hepatocytes | Assays for the regulation of a maceripion of white Enzyme are well-known in the art and may be well-known in the art and may be made or rountiely modified to assess the ability of polypeptics of the mivertion (reduding authodics and agonist or anagonists of the invention) to regulate transcription of mivertion to regulate transcription of invention of white Enzyme, a key enzyme in lipogenesis. Malic enzyme is lipogenesis. Malic enzyme is enzyme is expression is stimulted by insulin, expression is stimulted by insulin, expression is stimulted by insulin. | An ingle of vestigated indication is additionally preferred indication is additional ingleway preferred indication additional ingliny preferred indication additional ingliny preferred indication is complication associated with disherts (e.g., dishertic retinopathy, idiabetic nephropathy, iddeng disease (e.g., armal failure, nephropathy and/or other diseases and diseases and diseases and diseases and secretor in the Yearan Disoarders as section below, dishertic neuropathy, according by the Versell Disoarders as section below, dishertic neuropathy, experience of the Control of the Contr |

|                                                                                                                                     | iides<br>iin<br>seasc,<br>ske,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                     | general embodinents of the invention include using polypeptides of the invention (or authorities of the invention (or authorities) of the invention (or authorities) of the invention of the continuent of Viscular Disease, and Asthma.  Androxed-cross, Reseaussis, Stoke, and Asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                          |
| isolation. Cells undergo a pre-<br>adipocyte to adipose-like conversion<br>under appropriate differentiation<br>culture conditions. | ICAM-1 are yel for measuring expression of ICAM-1 are well-known in the art and may be used or roadinely of polypeptides of the invention of polypeptides of the invention) to polypeptides of the invention) to polypeptides of the invention) to measure (ICAM-1 expression include assays against ICAM-1 expression include assays and an are also assays that may be used ICAM-1 expression include assays and a polyperoperior (ICAM-1 expression include assays and a polyperoperior (ICAM-1 expression include assays ICAM-1 expression include assays and cransient (ICAM-1 in include assays are publicly assays that may be used according to these assays include | Kinase assay: measures the<br>phosphorylation of Elk-1, an<br>indication of activation of<br>extracellular signal regulated kinase<br>(ERK). ElKR pathway regulates cell |
|                                                                                                                                     | Production of ICAM-1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Inhibition of adipocyte<br>BRK signaling<br>pathway.                                                                                                                     |
|                                                                                                                                     | 438                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 440                                                                                                                                                                      |
|                                                                                                                                     | HCEWE20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HCGMD59                                                                                                                                                                  |
|                                                                                                                                     | 46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 36                                                                                                                                                                       |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | helphy peterred indication is additional indippy perferred indication is a display perferred indication is a complication associated with displayers (e.g., disbetic retimopathy, distract nephropathy, addition to phropathy, although in the complication in the complic |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| differentiation and differentiation and differentiation. Cells were preteated with SIN supernatures for 15-18 wore now, and then 100 and of installin was added to stimulate FISK kinase. The superhoryation of FIEL I was measured after a 20 minute measured after a 20 minute be used according to these assays are ATCCPs) and/or may be countied by the properties of the superhoryate deep that may be used according to these assays include a TTL-11 cells 3T3-L1 is an adherent adjocyte cell little may be used according to these assays include 3T3-L1 cells 13t3-L1 is an adherent move prediporey cell little that is a continuous substant of 3T3 continuous substant of an adipose-like state differentiation conditions known in the art. Cells state differentiation conditions known in the astronations known in the surem. (1974, the contents of which are incorporated by reference in its entirety. | Assays for measuring secretion of<br>insulin are well-known in the art and<br>may be used or runningly modified to<br>assess the allity of polyperides of<br>the invention (including authodies<br>the invention (including authodies<br>invention) to stimulate insulin<br>secretion; for example, insulin<br>secretion is measured by PMAT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 440                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HCGMD59                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 36                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| using anti-rat insulin antibodies.     | es.       | section below), diabetic neuropathy,   |
|----------------------------------------|-----------|----------------------------------------|
| Insulin secretion from pancreatic beta | atic beta | nerve disease and nerve damage         |
| cells is upregulated by glucose and    | c and     | (e.g., due to diabetic neuropathy),    |
| also by certain proteins/peptides, and | les, and  | blood vessel blockage, heart disease,  |
| disregulation is a key component in    | nent in   | stroke, impotence (e.g., due to        |
| diabetes. Exemplary assays that may    | hat may   | diabetic neuropathy or blood vessel    |
| be used or routinely modified to test  | to test   | blockage), seizures, mental            |
| for stimulation of insulin secretion   | ction     | confusion, drowsiness, nonketotic      |
| (from pancreatic cells) by             |           | hyperglycemic-hyperosmolar coma,       |
| polypeptides of the invention          |           | cardiovascular disease (e.g., heart    |
| (including antibodies and agonists or  | nists or  | disease, atherosclerosis,              |
| antagonists of the invention) include  | nclude    | microvascular disease, hypertension,   |
| assays disclosed in: Shimizu, H., et   | H, et     | stroke, and other diseases and         |
| al., Endocr J, 47(3):261-9 (2000);     | 90);      | disorders as described in the          |
| Salapatek, A.M., et al., Mol           |           | "Cardiovascular Disorders" section     |
| Endocrinol, 13(8):1305-17 (1999);      | 999);     | below), dyslipidemia, endocrine        |
| Filipsson, K., et al., Ann N Y Acad    | Acad      | disorders (as described in the         |
| Sci, 865:441-4 (1998); Olson, L.K.,    | , L.K.,   | "Endocrine Disorders" section          |
| et al., J Biol Chem, 271(28):16544-    | 6544-     | below), neuropathy, vision             |
| 52 (1996); and, Miraglia S ct. al.,    | al.,      | impairment (e.g., diabetic retinopathy |
| Journal of Biomolecular Screening,     | ening,    | and blindness), ulcers and impaired    |
| 4:193-204 (1999), the contents of      | Jo s      | wound healing, and infection (e.g.,    |
| each of which is herein incorporated   | orated    | infectious diseases and disorders as   |
| by reference in its entirety.          |           | described in the "Infectious           |
| Pancreatic cells that may be used      | pas       | Diseases" section below, especially    |
| according to these assays are publicly | publicly  | of the urinary tract and skin), carpal |
| available (e.g., through the ATCCTM)   | ICCTM)    | me a                                   |
| and/or may be routinely generated.     | rated.    | contracture). An additional            |
| Exemplary pancreatic cells that may    | at may    | highly preferred indication is obesity |
| be used according to these assays      | says      | and/or complications associated with   |
| include HITT15 Cells. HITT15 are       | 15 are    | obesity. Additional highly preferred   |
| an adherent epithelial cell line       |           | indications include weight loss or     |
| established from Syrian hamster islet  | ter islet | alternatively, weight gain. Additional |
| cells transformed with SV40. These     | These     | highly preferred indications are       |
| cells express glucagon, somatostatin,  | ostatin,  | complications associated with insulin  |
| and glucocorticoid receptors. The      | The       | resistance.                            |
| cells secrete insulin, which is        |           |                                        |

|                                                                                                                                                                                                                                   | A highly preferred infication is idiabetes mellins; an additional inguishers enrellins; an additional ingulation enrellins; an additional ingulation enrellins; an additional displace; e.g., dished; retinopathy, dishey disease; displace; e.g., dished; retinopathy, dishey disease; dee, renal failure, hephropathy and control diseases and disorders as adescribed in the "Renal Disorders; a reave disease and neave damage (e.g., renal failure, hephropathy, probed vessel blockage, heard disease, day, displace; mercured (e.g., due to disched; menoropathy or blood vessel blockage, heard disease, capterior neuropathy or blood vessel blockage, heard disease, mental disease, mental disease, superconstant committee, proposation of the disease; and menosition of the disease; and menosition of the disease; and menosition of the diseases and disease; and promoves and teases, hypertension, assunce, and other diseases and elsewhed in the Candiovascular Disorders' section disorders (as described in the disorders' section below), neuropathy, vision below), neuropathy, vision and invarient of the disease and heaviers and invarient of the disease and the  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| stimulated by glucose and glucagon and glucagon and suppressed by somanostatin or glucocorticoids. ATTC#C4.7777 Refs. Lord and Ashronti. Biochem. 1, 219-547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981. | Assessy for the regulation of viability Assessy for the regulation of cells in vitus and positieration of cells in vitus are discounted in the art and may be the chain of the condition of the cells in vitus to the chain of the |
|                                                                                                                                                                                                                                   | Regulation of Viability<br>and proliferation of<br>puncreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                   | 144                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                   | HCNDR47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                   | 37                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                      | 2 2 2                                   |                                        |
|----|---------|-----|----------------------|-----------------------------------------|----------------------------------------|
|    |         |     |                      | its entirety. Fancteauc cens that may   | would nearing, and miccuon (e.g.,      |
|    |         |     |                      | be used according to these assays are   | infectious diseases and disorders as   |
|    |         |     |                      | publicly available (e.g., through the   | described in the "Infectious           |
|    |         |     |                      | ATCCTM) and/or may be routinely         | Diseases" section below, especially    |
|    |         |     |                      | generated. Exemplary pancreatic         | of the urinary tract and skin), carpal |
|    |         |     |                      | cells that may be used according to     | tunnel syndrome and Dupuytren's        |
|    |         |     |                      | these assays include rat INS-1 cells.   | contracture). An additional highly     |
|    |         |     |                      | INS-1 cells are a semi-adherent cell    | preferred indication is obesity and/or |
|    |         |     |                      | line established from cells isolated    | complications associated with          |
|    |         |     |                      | from an X-ray induced rat               | obesity. Additional highly preferred   |
|    |         |     |                      | transplantable insulinoma. These        | indications include weight loss or     |
|    |         |     |                      | cells retain characteristics typical of | alternatively, weight gain. Additional |
|    |         |     |                      | native pancreatic beta cells including  | highly preferred indications are       |
|    |         |     |                      | glucose inducible insulin secretion.    | complications associated with insulin  |
|    |         |     |                      | References: Asfari et al.               | resistance.                            |
|    |         |     |                      | Endocrinology 1992 130:167.             |                                        |
|    | HCNDR47 | 441 | Production of RANTES | RANTES FMAT. Assays for                 |                                        |
| 37 |         |     | in endothelial cells | immunomodulatory proteins that          |                                        |
|    |         |     | (such as human       | induce chemotaxis of T cells,           |                                        |
|    |         |     | umbilical vein       | monocytes, and eosinophils are well     |                                        |
|    |         |     | endothelial cells    | known in the art and may be used or     |                                        |
|    |         |     | (HUVEC))             | routinely modified to assess the        |                                        |
|    |         |     |                      | ability of polypeptides of the          |                                        |
|    |         |     |                      | invention (including antibodies and     |                                        |
|    |         |     |                      | agonists or antagonists of the          |                                        |
|    |         |     |                      | invention) to mediate                   |                                        |
|    |         |     |                      | immunomodulation, induce                |                                        |
|    |         |     |                      | chemotaxis, and/or mediate humoral      |                                        |
|    |         |     |                      | or cell-mediated immunity.              |                                        |
|    |         |     |                      | Exemplary assays that test for          |                                        |
|    |         |     |                      | immunomodulatory proteins evaluate      |                                        |
|    |         |     |                      | the production of cytokines, such as    |                                        |
|    |         |     |                      | RANTES, and the induction of            |                                        |
|    |         |     |                      | chemotactic responses in immune         |                                        |
|    |         |     |                      | cells. Such assays that may be used     |                                        |
|    |         |     |                      | or routinely modified to test           |                                        |
|    |         |     |                      | immunomodulatory activity of            |                                        |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly perfected embediament<br>of the invention includes a method<br>for stimulating adjacyte.<br>In consideration An alternative highly<br>preferred embediament of the<br>preferred embediament of the<br>inhibiting adjacycyc proliferation.<br>A highly preferred embediament of<br>the invention includes a method for<br>the invention includes a method for<br>any and alternative bindy preferred and<br>alternative bindy preferred and alternative includes are method for<br>An alternative bindy preferred and alternative bindy preferred |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (including authorides and ageniss on authorides and ageniss on authorides and ageniss on authorides and ageniss on authorides of the invention include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-1 Authoride 134, Science 270(234); RII-1815 et al., Science 270(234); RII-1816 et al., Science 2600, which are lowed to the control to the cont | finance sawy, frience sawy, for example at IR-I kinnee sawy, for ER-K signal transduction that regulate cell proliferation of differentiation are well known in the art and may be and or rountinely modified to assess the ability of bodypeptides of the remetion (including anthodics and agonists or antagonists of the assessing the ability of high section of the control or thinhit cell proliferation, activation, and                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of Activation of Adiposper ERK Adiposper Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 442                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCNSB61                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 38                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| in in                                                                                                                                                        | _ | differentiation. Exemplary assays for ERK kinase activity that may be used  |                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| to . t                                                                                                                                                       |   | or routinely modified to test ERK kinase-induced activity of                | adipocyte differentiation. A                                             |
| o f L (2)                                                                                                                                                    |   | polypeptides of the invention                                               | invention includes a method for                                          |
| a. 6 466 + 1 4 0                                                                                                                                             |   | (including antibodies and agonists or                                       | stimulating (e.g., increasing)                                           |
| g. 4.5                                                                                                                                                       |   | anagomsts of the inventory) menue<br>the assays disclosed in Forrer et al., | aupocyte activation. An ancinative<br>highly preferred embodiment of the |
| g. 4,5,0 a                                                                                                                                                   |   | Biol Chem 379(8-9):1101-1110                                                | invention includes a method for                                          |
| A.C. 11 0.                                                                                                                                                   |   | (1998); Le Marchand-Brustel Y, Exp                                          | inhibiting the activation of (e.g.,                                      |
| A                                                                                                                                                            |   | Clin Endocrinol Diabetes                                                    | decreasing) and/or inactivating                                          |
| 0 t : 't '%                                                                                                                                                  |   | 107(2):126-132 (1999); Kyriakis JM,                                         | 1                                                                        |
|                                                                                                                                                              |   | Chang and Karin Nature                                                      | disorders (e.g. as described below                                       |
| ti _ ti 0.                                                                                                                                                   |   | 410(6824):37-40 (2001); and Cobb                                            | under "Endocrine Disorders").                                            |
| 10 10 11 11 11 11 11 11 11 11 11 11 11 1                                                                                                                     |   | MH, Prog Biophys Mol Biol 71(3-                                             | Highly preferred indications also                                        |
| 1 20 II                                                                                                                                                      |   | 4):479-500 (1999); the contents of                                          | include neoplastic diseases (e.g.,                                       |
| 1 30 H 1                                                                                                                                                     |   | each of which are herein                                                    | lipomas, liposarcomas, and/or as                                         |
| =                                                                                                                                                            |   | incorporated by reference in its                                            | described below under                                                    |
| - 4 S -                                                                                                                                                      |   | entirety. Mouse adipocyte cells that                                        | "Hyperproliferative Disorders").                                         |
| c 4 8 -                                                                                                                                                      |   | may be used according to these                                              | Preferred indications include blood                                      |
| . 4 % .                                                                                                                                                      |   | assays are publicly available (e.g.,                                        | disorders (e.g., hypertension,                                           |
| . 30 E                                                                                                                                                       |   | through the ATCC <sup>TM</sup> ). Exemplary                                 | congestive heart failure, blood vessel                                   |
| is an ell in of dergo                                                                                                                                        |   | mouse adipocyte cells that may be                                           | blockage, heart disease, stroke,                                         |
|                                                                                                                                                              |   | used according to these assays                                              | impotence and/or as described below                                      |
|                                                                                                                                                              |   | melude 313-L1 cells. 313-L1 is an                                           | under immune Acuvity,                                                    |
|                                                                                                                                                              |   | adherent mouse preadipocyte cell                                            | "Cardiovascular Disorders", and/or                                       |
| under "Immune Activi disorders (e.g., as desc under "Neural Activity Neurological Diseases infection (e.g., as desc under "Infectious Dise                   |   | June that is a continuous suostrain or<br>3T3 fibroblast cells developed    | disorders (e.g., as described below                                      |
| disorders (e.g., as desc<br>under "Neural Activity<br>Neurological Diseases'<br>infection (e.g., as desc<br>under "Infectious Dise<br>A highly preferred ind |   | through clonal isolation and undergo                                        | under "Immune Activity"), neural                                         |
| under "Neural Activity Neurological Diseases' infection (e.g., as descr under "Infectious Dise A highly preferred ind                                        |   | a pre-adipocyte to adipose-like                                             | disorders (e.g., as described below                                      |
| Neurological Diseases<br>infection (e.g., as descr<br>under "Infectious Dise<br>A highly preferred ind                                                       |   | conversion under appropriate                                                | under "Neural Activity and                                               |
| infection (e.g., as desci<br>under "Infectious Dise<br>A highly preferred ind                                                                                |   | differentiation conditions known in                                         | Neurological Diseases"), and                                             |
| Dise<br>ind                                                                                                                                                  |   | the art.                                                                    | infection (e.g., as described below                                      |
| ind                                                                                                                                                          |   |                                                                             | under "Infectious Disease").                                             |
|                                                                                                                                                              |   |                                                                             | ind                                                                      |

| _ |  | highly preferred indication is a       |
|---|--|----------------------------------------|
|   |  | complication associated with           |
|   |  | diabetes (e.g., diabetic retinopathy,  |
|   |  | diabetic nephropathy, kidney disease   |
|   |  | (e.g., renal failure, nephropathy      |
|   |  | and/or other diseases and disorders as |
|   |  | described in the "Renal Disorders"     |
|   |  | section below), diabetic neuropathy,   |
|   |  | nerve disease and nerve damage         |
|   |  | (e.g., due to diabetic neuropathy),    |
|   |  | blood vessel blockage, heart disease,  |
|   |  | stroke, impotence (e.g., due to        |
|   |  | diabetic neuropathy or blood vessel    |
|   |  | blockage), seizures, mental            |
|   |  | confusion, drowsiness, nonketotic      |
|   |  | hyperglycemic-hyperosmolar coma,       |
|   |  | cardiovascular disease (e.g., heart    |
|   |  | disease, atherosclerosis,              |
|   |  | microvascular disease, hypertension,   |
|   |  | stroke, and other diseases and         |
|   |  | disorders as described in the          |
|   |  | "Cardiovascular Disorders" section     |
|   |  | below), dyslipidemia, endocrine        |
|   |  | disorders (as described in the         |
|   |  | "Endocrine Disorders" section          |
|   |  | below), neuropathy, vision             |
|   |  | impairment (e.g., diabetic retinopathy |
|   |  | and blindness), ulcers and impaired    |
|   |  | wound healing, infection (e.g.,        |
|   |  | infectious diseases and disorders as   |
|   |  | described in the "Infectious           |
|   |  | Diseases" section below (particularly  |
|   |  | of the urinary tract and skin). An     |
|   |  | additional highly preferred indication |
|   |  | is obesity and/or complications        |
|   |  | associated with obesity. Additional    |
|   |  | highly preferred indications include   |

|    |         |     |                               |                                                                                                                                                                                                            | weight loss or alternatively, weight gain, weight loss or alternatively, weight gain. Additional highly weight sectored indications a feet by weight sections are complications associated with insulince and the maculoskedeal systems including myophies, macular dystophy, and or as described system. Additional highly preferred indications including myophies, macular dystophy, and or as described by a suppretension, consumy attery disease, dystipidenia, gallstones, organization highly preferred indications include disease, dystipidenia, gallstones, consolvantials, dependents, and thrusts, central disease, dystipidenia, gallstones, propersion, and charter and breast, bromphorm, leakemia and breast bromen and lipostroums. Other propersion include inpostruct indications include hypophistic conditions, such as, for example, hypophists, menghos, such as, for example, hypophists, menghos, such as, for example, hypophists, menghosis, men |
|----|---------|-----|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 38 | HCNSB61 | 442 | Endothelial Cell<br>Apoptosis | Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypepties of the invention (including antibodies and agoniss or | andor dysplasis.  A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| - 1 | endomenial cell growth. A nigniy | preferred embodiment of the       | invention includes a method for      | stimulating endothelial cell     | proliferation. An alternative highly | preferred embodiment of the          | invention includes a method for | inhibiting endothelial cell           | proliferation. A highly               | preferred embodiment of the  | invention includes a method for | stimulating apoptosis of endothelial  | cells. An alternative highly preferred | embodiment of the invention         | includes a method for inhibiting (e.g., | decreasing) apoptosis of endothelial  | cells. A highly preferred        | embodiment of the invention    | includes a method for stimulating     | angiogenisis. An alternative highly  | preferred embodiment of the             | invention includes a method for | inhibiting angiogenesis. A highly    | preferred embodiment of the  | invention includes a method for      | reducing cardiac hypertrophy. An  | alternative highly preferred      | embodiment of the invention        | includes a method for inducing        | cardiac hypertrophy. Highly           | preferred indications include         | neoplastic diseases (e.g., as described | below under "Hyperproliferative | Disorders"), and disorders of the | cardiovascular system (e.g., heart | disease, congestive heart failure, | hypertension, aortic stenosis, |
|-----|----------------------------------|-----------------------------------|--------------------------------------|----------------------------------|--------------------------------------|--------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|------------------------------|---------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------------|---------------------------------------|----------------------------------|--------------------------------|---------------------------------------|--------------------------------------|-----------------------------------------|---------------------------------|--------------------------------------|------------------------------|--------------------------------------|-----------------------------------|-----------------------------------|------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|---------------------------------|-----------------------------------|------------------------------------|------------------------------------|--------------------------------|
|     | antagonists of the invention) to | promote caspase protease-mediated | apoptosis. Induction of apoptosis in | endothelial cells supporting the | vasculature of tumors is associated  | with tumor regression due to loss of | tumor blood supply. Exemplary   | assays for caspase apoptosis that may | be used or routinely modified to test | capase apoptosis activity of | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include  | the assays disclosed in Lee et al., | FEBS Lett 485(2-3): 122-126 (2000);     | Nor et al., J Vasc Res 37(3): 209-218 | (2000); and Karsan and Harlan, J | Atheroscler Thromb 3(2): 75-80 | (1996); the contents of each of which | are herein incorporated by reference | in its entirety. Endothelial cells that | may be used according to these  | assays are publicly available (e.g., | through commercial sources). | Exemplary endothelial cells that may | be used according to these assays | include bovine aortic endothelial | cells (bAEC), which are an example | of endothelial cells which line blood | vessels and are involved in functions | that include, but are not limited to, | angiogenesis, vascular permeability,    | vascular tone, and immune cell  | extravasation.                    |                                    |                                    |                                |
|     |                                  |                                   |                                      |                                  |                                      |                                      |                                 |                                       |                                       |                              |                                 |                                       |                                        |                                     |                                         |                                       |                                  |                                |                                       |                                      |                                         |                                 |                                      |                              |                                      |                                   |                                   |                                    |                                       |                                       |                                       |                                         |                                 |                                   |                                    |                                    |                                |
|     |                                  |                                   |                                      |                                  |                                      |                                      |                                 |                                       |                                       |                              |                                 |                                       |                                        |                                     |                                         |                                       |                                  |                                |                                       |                                      |                                         |                                 |                                      |                              |                                      |                                   |                                   |                                    |                                       |                                       |                                       |                                         |                                 |                                   |                                    |                                    |                                |
|     |                                  |                                   |                                      |                                  |                                      |                                      |                                 |                                       |                                       |                              |                                 |                                       |                                        |                                     |                                         |                                       |                                  |                                |                                       |                                      |                                         |                                 |                                      |                              |                                      |                                   |                                   |                                    |                                       |                                       |                                       |                                         |                                 |                                   |                                    |                                    |                                |
|     |                                  |                                   |                                      |                                  |                                      |                                      |                                 |                                       |                                       |                              |                                 |                                       |                                        |                                     |                                         |                                       |                                  |                                |                                       |                                      |                                         |                                 |                                      |                              |                                      |                                   |                                   |                                    |                                       |                                       |                                       |                                         |                                 |                                   |                                    |                                    |                                |

|  | oibaco   | and invasion and and and and            |
|--|----------|-----------------------------------------|
|  | - Carren | myopamy, varvam                         |
|  | regurg   | regurgitation, left ventricular         |
|  | dysfu    | dysfunction, atherosclerosis and        |
|  | athero   | atherosclerotic vascular disease,       |
|  | diabet   | diabetic nephropathy, intracardiac      |
|  | shunt    | shunt, cardiac hypertrophy,             |
|  | myoc     | myocardial infarction, chronic          |
|  | hemor    | hemodynamic overload, and/or as         |
|  | descri   | described below under                   |
|  | "Card    | "Cardiovascular Disorders"). Highly     |
|  | lprefer  | preferred indications include           |
|  | cardio   | cardiovascular, endothelial and/or      |
|  | angio    | angiogenic disorders (e.g., systemic    |
|  | disord   | disorders that affect vessels such as   |
|  | diabet   | diabetes mellitus, as well as diseases  |
|  | of the   | of the vessels themselves, such as of   |
|  | the ar   | the arteries, capillaries, veins and/or |
|  | lympl    | lymphatics). Highly preferred are       |
|  | indica   | indications that stimulate              |
|  | angio    | angiogenesis and/or                     |
|  | cardio   | cardiovascularization. Highly           |
|  | prefer   | preferred are indications that inhibit  |
|  | angio    |                                         |
|  | cardio   | cardiovascularization. Highly           |
|  | nejerd   | preferred indications include           |
|  | antian   | antiangiogenic activity to treat solid  |
|  | tumor    | tumors, leukemias, and Kaposi"s         |
|  | sarcor   | sarcoma, and retinal disorders.         |
|  | Highl    | Highly preferred indications include    |
|  | ldoəu    | neoplasms and cancer, such as,          |
|  | Kapos    | Kaposi"s sarcoma, hemangioma            |
|  | (capil   | (capillary and cavernous), glomus       |
|  | tumor    | tumors, telangiectasia, bacillary       |
|  | angion   | angiomatosis,                           |
|  | hemai    | hemangioendothelioma,                   |
|  | angio    | angiosarcoma,                           |
|  | haems    | haemangiopericytoma,                    |

|  | lymphangioma, lymphangiosarcoma.       |
|--|----------------------------------------|
|  | Hiohly preferred indications also      |
|  | include cancers such as, prostate,     |
|  | breast, lung, colon, pancreatic,       |
|  | esophageal, stomach, brain, liver,     |
|  | and urinary cancer. Preferred          |
|  | indications include benign             |
|  | dysproliferative disorders and pre-    |
|  | neoplastic conditions, such as, for    |
|  | example, hyperplasia, metaplasia,      |
|  | and/or dysplasia. Highly               |
|  | preferred indications also include     |
|  | arterial disease, such as,             |
|  | atherosclerosis, hypertension,         |
|  | coronary artery disease,               |
|  | inflammatory vasculitides,             |
|  | Reynaud"s disease and Reynaud"s        |
|  | phenomenom, aneurysms, restenosis;     |
|  | venous and lymphatic disorders such    |
|  | as thrombophlebitis, lymphangitis,     |
|  | and lymphedema; and other vascular     |
|  | disorders such as peripheral vascular  |
|  | disease, and cancer. Highly            |
|  | preferred indications also include     |
|  | trauma such as wounds, burns, and      |
|  | injured tissue (e.g., vascular injury  |
|  | such as, injury resulting from balloon |
|  | angioplasty, and atheroschlerotic      |
|  | lesions), implant fixation, scarring,  |
|  | ischemia reperfusion injury,           |
|  | rheumatoid arthritis, cerebrovascular  |
|  | disease, renal diseases such as acute  |
|  | renal failure, and osteoporosis.       |
|  | Additional highly preferred            |
|  | indications include stroke, graft      |
|  | rejection, diabetic or other           |
|  | retinopathies, thrombotic and          |

|         |          |                                                                                                     |                                                                                                                                                                                                                                                                                                                                                        | coagulative disorders, vascularitis, lymph augogenesis, sevual disorders, age-related macular degeneration, and treatment prevention, and treatment prevention of endomericisis and prevention of endomericisis and related conditions. Additional highly related conditions. Additional highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------|----------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | :        |                                                                                                     |                                                                                                                                                                                                                                                                                                                                                        | intervent indications include from the control includes include the control for the control fo |
| HCUIM65 | 445<br>2 | Regulation of<br>transcription via<br>DMEFI response<br>clement in adipocytes<br>and pre-adipocytes | transaction through the DMFFI<br>transactipion through the DMFFI<br>stronges element are well-known in<br>the art and may be used or nontinely<br>modified to assess the ability of<br>polypeptides of the invention<br>(including anthodies and agoniss or<br>analogies and agoniss or<br>agonism of the invention to<br>activate the DMFFI response. | helip preferent aufheision is<br>diabetes mellitus. Additional lighty<br>perferent diabetions include<br>perferent diabetions include<br>perferent diabetions associated with<br>diabetes (e.g., diabetic retinopathy,<br>diabetes (e.g., retal failure, heptropathy<br>(e.g., retal failure, heptropathy<br>described in the "Retal Disorders is                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| section below), diabetic neuropathy,  | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental      | confusion, drowsiness, nonketotic     | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,     | microvascular disease, hypertension,  | stroke, and other diseases and      | disorders as described in the | "Cardiovascular Disorders" section  | below), dyslipidemia, endocrine     | disorders (as described in the     | "Endocrine Disorders" section       | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious      | Diseases" section below, especially | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications    | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly preferred | indications are complications  | associated with insulin resistance. |                                     |                                  |                               |
|---------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|----------------------------------|---------------------------------------|----------------------------------|-------------------------------------|-------------------------------|---------------------------------------|-------------------------------------|-------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|----------------------------------------|------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------|
| element in a reporter construct (such | as that containing the GLUT4   | promoter) and to regulate insulin   | production. The DMEF1 response        | element is present in the GLUT4 | promoter and binds to MEF2          | transcription factor and another | transcription factor that is required | for insulin regulation of Glut4  | expression in skeletal muscle.      | GLUT4 is the primary insulin- | responsive glucose transporter in fat | and muscle tissue. Exemplary assays | that may be used or routinely | modified to test for DMEF1 response | element activity (in adipocytes and | pre-adipocytes) by polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed    | inThai, M.V., et al., J Biol Chem,  | 273(23):14285-92 (1998); Mora, S.,  | et al., J Biol Chem, 275(21):16323-8 | (2000); Liu, M.L., et al., J Biol | Chem, 269(45):28514-21 (1994);      | "Identification of a 30-base pair  | regulatory element and novel DNA       | binding protein that regulates the | human GLUT4 promoter in             | transgenic mice", J Biol Chem. 2000  | Aug 4;275(31):23666-73; Berger, et   | al., Gene 66:1-10 (1988); and,    | Cullen, B., et al., Methods in | Enzymol. 216:362-368 (1992), the    | contents of each of which is herein | incorporated by reference in its | entirety. Adipocytes and pre- |
|                                       |                                |                                     |                                       |                                 |                                     |                                  |                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |
|                                       |                                |                                     |                                       |                                 |                                     |                                  |                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | obesity and/or complications is obesity and/or complications obesity and/or complications obesity and/or complications obesity. Additional highly preferred indications include weight loss or alternatively, weight weight loss or alternatively, weight and a state of the properties of the profession of allowers meditius. An additional highly preferred indication is altowers meditius. An indication is altowers meditius. An additional highly preferred indication is a complication associated with its example of the complication associated with disheder of example allowers of the complication and or other diseases and diseases and interve damage exection belowly, diabetic neuropathy, or blood vessel biokage, hearing the care of dishedic neuropathy or blood vessel biokage, hearing an or blood vessel diabetic neuropathy are blood vessel diabetic neuropathy and or blood vessel diabetic neuropathy are blood vessel diabetic neuropathy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| adipocytes that may be used accounting to these assays are publicly available (e.g., through the ATCCP) and and or may be nothing by generated accounting to these assays include the Escenplary cells that may be used accounting to these assays include the accountinuous spreadipocyte cell film white, is an adherent mouse preadipocyte cell film broblass develored through chan is solution. These cells undergo a pre- adipocyte to adipose-like conversion adipocyte to adipose-like conversion culture capropriate differentiation culture conditions. | transcription through the cAMP  transcription through the cAMP  the art and may be used or routinely  the art and may be used or routinely  the art and may be used or routinely  modified to assess the ability of  modified the assess the ability of  modifie |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | transcription through<br>cacher response<br>element ((RE) in pre-<br>adiposyes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 445                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HCUIMIGS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| gain. An additional highly preferred indication is diabetes mellitus. An | additional highly preferred indication | is a complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders"   | section below), diabetic neuropathy,  | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | ÷                                      | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic   | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart  | disease, atherosclerosis,          | microvascular disease, hypertension, | stroke, and other diseases and  | disorders as described in the | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine      | disorders (as described in the     | "Endocrine Disorders" section   | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g.,      | infectious diseases and disorders as | described in the "Infectious         | Discases" section below). Additional | highly preferred indications are | complications associated with insulin | resistance. |
|--------------------------------------------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------------|----------------------------------|--------------------------------------|------------------------------------|--------------------------------------|---------------------------------|-------------------------------|----------------------------------------|--------------------------------------|------------------------------------|---------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|------------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|-------------|
| ability of polypeptides of the invention (including antibodies and       | agonists or antagonists of the         | invention) to regulate the serum  | response factors and modulate the     | expression of genes involved in      | growth. Exemplary assays for      | transcription through the SRE that     | may be used or routinely modified to | test SRE activity of the polypeptides | of the invention (including antibodies | and agonists or antagonists of the  | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in         | Enzymol 216:362-368 (1992); | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); and     | Black et al., Virus Genes 12(2):105- | 117 (1997), the content of each of | which are herein incorporated by     | reference in its entirety. Pre- | adipocytes that may be used   | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary mouse adipocyte cells | that may be used according to these | assays include 3T3-L1 cells. 3T3-L1    | is an adherent mouse preadipocyte   | cell line that is a continuous substrain | of 3T3 fibroblast cells developed    | through clonal isolation and undergo | a pre-adipocyte to adipose-like      | conversion under appropriate     | differentiation conditions known in   | the art.    |
|                                                                          |                                        |                                   |                                       | _                                    | _                                 | _                                      |                                      | _                                     | _                                      | _                                   | _                                      | _                                   | _                                   |                             |                                     |                                  | _                                    | _                                  | _                                    |                                 | _                             |                                        | _                                    | _                                  | _                               |                                     | _                                      |                                     |                                          |                                      | _                                    | _                                    | _                                | _                                     |             |
|                                                                          |                                        |                                   |                                       |                                      |                                   |                                        |                                      |                                       |                                        |                                     |                                        |                                     |                                     |                             |                                     |                                  |                                      |                                    |                                      |                                 |                               |                                        |                                      |                                    |                                 |                                     |                                        |                                     |                                          |                                      |                                      |                                      |                                  |                                       | _           |
|                                                                          |                                        |                                   |                                       |                                      |                                   |                                        |                                      |                                       |                                        |                                     |                                        |                                     |                                     |                             |                                     |                                  |                                      |                                    |                                      |                                 |                               |                                        |                                      |                                    |                                 |                                     |                                        |                                     |                                          |                                      |                                      |                                      |                                  |                                       |             |

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| Reporter Assay; construct contains sequence of squadeney and config sequence of squadeney symbenses, the first specific biosymben in the following the sequence of biosymbene belongs and the sequence of biosymbene belongs and the sequence of the sequence | seaso for measuring estellant flux are woll-known in the art and may be used or routinely modified to assess the ability of polyperdides of the invention (including antibodies and invention) (including antibodies and invention) to mobilize calcium. For assessing the Ref assist may be used to measure influx of calcium, to concentrations of cytosobic calcium concentrations of cytosobic calcium concentrations of cytosobic calcium compared to much higher compared to much higher centroclibita culcium. Extracellatar calcium. Extracellatar factors are cause an influx of calcium responsave signaling pluty and additions. Exemplary assays that functions. Exemplary assays that much be used or cuntively modified to measure calcium flux by                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Inhibition of squatere synthesise gene transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Simulation of Calcium Plax in pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 445                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 445                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| нсими                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HCUIM65                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 41                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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| stroke, and other diseases and characteristics, and control diseases and characters as described in the "Cardiovascular Disorders" section the object of sease and control disorders (see described in the disorders (see described in the disorders (see described in the characters) section below), neuropathy, vision below), neuropathy, vision below), neuropathy, vision below), neuropathy, vision disorders (see all imported to the characters) and inception (e.g., infections tisoses), allocars and incidences as described in the "Infections tisoses," and control below, copecially of the united syndrome helow, copecially of the united syndrome and Dapayeers is controlled to the wind Dapayeers of the united syndrome in Dapayeers is controlled in the "Infections is obesity and on complications associated with incultin resistance.  Additional highly preferred in the object of the complications as ecouplications as are complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious |
| (including antibodies and agoniss or antibodies and agoniss or antipodies of the invention include assays disclosed in: Salm i.S. et al., deborrinology, 216(10)-5489-601.  [1995], Mchanish at et al., [2607-2866-6].  [1995], Richardson SB, et al., Cell and the control of the c | This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of<br>transcription through<br>GATA-3 response<br>element in immune                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 445                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | нсиім65                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 41                                                                                                                                          |

| disease as described below under      | information and inflammatory    | disorders. Preferred indications also | include blood disorders (e.g., as | described below under "Immune | Activity", "Blood-Related         | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications    | include autoimmune diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis    | and/or as described below) and      | immunodeficiencies (e.g., as      | described below). Preferred     | indications include neoplastic       | discases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary    | tract cancers and/or as described     | below under "Hyperproliferative    | Disorders"). Other preferred    | indications include benign | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | thrombocytopenia, leukemias,       | Hodgkin's disease, acute            | lymphocytic anemia (ALL),           | plasmacytomas, multiple myeloma,     | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, sepsis, neutropenia,   |
|---------------------------------------|---------------------------------|---------------------------------------|-----------------------------------|-------------------------------|-----------------------------------|------------------------------------|---------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|
| cells has been linked to cytokine and | the activation of transcription | through the GATA3 response            | element are well-known in the art | and may be used or routinely  | modified to assess the ability of | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to   | regulate GATA3 transcription factors | and modulate expression of mast cell | genes important for immune response | development. Exemplary assays for | transcription through the GATA3 | response element that may be used or | routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its    | entirety. Mast cells that may be used |
| cells (such as mast                   | cens).                          |                                       |                                   |                               |                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |
|                                       |                                 |                                       |                                   |                               |                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |

|   |         |     |                                                                                                                              | coording to these saseys are publicly available (e.g., through the available (e.g., through the available (e.g., through the t | of immure reactions to present<br>of immure reactions to transplanted<br>organs and issues, hencophilia,<br>hyperoagulation, disheres melitins,<br>endocardis, meninglis, and Lyme<br>Disease.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---|---------|-----|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4 | HCUIM65 | 445 | Activation of Macaragian of Macaragian of Macaragian through NFA tropous of the demont in immune oells (such as mast cells). | This reporter uses y measures activation of the NFAT signaling pathway in HMC-1 human mast cell mass of the Activation of NFAT in mast cells have been linked to optoking and cells has been linked to optoking and the activation of transcription. Assays for the activation of transcription of the activation of transcription of the activation of transcription in the art activation of transcription in the art and may be used or routinely a modified to assess the ability of polypoptides of the invention) to modified to assess the ability of polypoptides of the invention) to regulate VPAT transcription factors involved in immunomodulatory incurrent and many be used or programment of the publication. Resembling the NFAT reasons element that may be used or routinely modified to test NFAT reasons clement that may be used or routinely modified to test NFAT reasons clement that may be used or routinely modified to test NFAT reasons clement and may be used or routinely modified to test NFAT.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Highly preferred indications include altergy selfma, and himits.  Additional preferred indications include inclosin (e.g., in mirections disease as described below under friedrious Diseases,), and inflammation and inflammatory diseases, and inflammatory additions also include blood sixoders (e.g., as seeched below under "Immune Activity", "Blood-Related Diseases and described below include undo include undo include undo include and include including six preferred indications include neoplastic described blook) and immunodeliciencies (e.g., in medanoma, prostate breast, lung medanoma, prostate breast, lung sommed, and canceres and on se described |

|         |     |                       | assave disclosed in Berger of al           | Disorders") Other preferred             | _ |
|---------|-----|-----------------------|--------------------------------------------|-----------------------------------------|---|
|         |     |                       | Gene 66-1-10 (1998): Cullen and            | indications include henion              |   |
|         |     |                       | Malm, Methods in Enzymol                   | dysproliferative disorders and pre-     |   |
|         |     |                       | 216:362-368 (1992); Henthorn et al.,       | neoplastic conditions, such as, for     |   |
|         |     |                       | Proc Natl Acad Sci USA 85:6342-            | example, hyperplasia, metaplasia,       |   |
|         |     |                       | 6346 (1988); De Boer et al., Int J         | and/or dysplasia. Preferred             |   |
|         |     |                       | Biochem Cell Biol 31(10):1221-1236         | indications include anemia,             |   |
|         |     |                       | (1999); Ali et al., J Immunol              | pancytopenia, leukopenia,               |   |
|         |     |                       | 165(12):7215-7223 (2000);                  | thrombocytopenia, leukemias,            |   |
|         |     |                       | Hutchinson and McCloskey, J Biol           | Hodgkin's disease, acute                |   |
|         |     |                       | Chem 270(27):16333-16338 (1995),           | lymphocytic anemia (ALL),               |   |
|         |     |                       | and Turner et al., J Exp Med               | plasmacytomas, multiple myeloma,        |   |
|         |     |                       | 188:527-537 (1998), the contents of        | Burkitt's lymphoma, arthritis, AIDS,    |   |
|         |     |                       | each of which are herein                   | granulomatous disease, inflammatory     |   |
|         |     |                       | incorporated by reference in its           | bowel disease, sepsis, neutropenia,     |   |
|         |     |                       | entirety. Mast cells that may be used      | neutrophilia, psoriasis, suppression    |   |
|         |     |                       | according to these assays are publicly     | of immune reactions to transplanted     |   |
|         |     |                       | available (e.g., through the               | organs and tissues, hemophilia,         |   |
|         |     |                       | ATCC <sup>TM</sup> ). Exemplary human mast | hypercoagulation, diabetes mellitus,    |   |
|         |     |                       | cells that may be used according to        | endocarditis, meningitis, and Lyme      |   |
|         |     |                       | these assays include the HMC-1 cell        | Disease.                                |   |
|         |     |                       | line, which is an immature human           |                                         |   |
|         |     |                       | mast cell line established from the        |                                         |   |
|         |     |                       | peripheral blood of a patient with         |                                         |   |
|         |     |                       | mast cell leukemia, and exhibits           |                                         |   |
|         |     |                       | many characteristics of immature           |                                         |   |
| HCUIM65 | 445 | Activation of         | This reporter assay measures               | Highly preferred indication includes    | _ |
|         |     | transcription through | activation of the NFkB signaling           | allergy, asthma, and rhinitis.          |   |
|         |     | NFKB response         | pathway in HMC-1 human mast cell           | Additional highly preferred             |   |
|         |     | element in immune     | line. Activation of NFkB in mast           | indications include infection (e.g., an |   |
|         |     | cells (such as mast   | cells has been linked to production of     | infectious disease as described below   |   |
|         |     | cells).               | certain cytokines, such as IL-6 and        | under "Infectious Disease"), and        |   |
|         |     |                       | IL-9. Assays for the activation of         | inflammation and inflammatory           |   |
|         |     |                       | transcription through the NFKB             | disorders. Preferred indications        |   |
|         |     |                       | response element are well-known in         | include immunological and               |   |
|         |     |                       | the art and may be used or routinely       | hempatopoietic disorders (e.g., as      | _ |

|  | modified to assess the ability of          | described below under "Immune          |
|--|--------------------------------------------|----------------------------------------|
|  | polypeptides of the invention              | Activity", and "Blood-Related          |
|  | (including antibodies and agonists or      | Disorders"). Preferred indications     |
|  | antagonists of the invention) to           | also include autoimmune diseases       |
|  | regulate NFKB transcription factors        | (e.g., rheumatoid arthritis, systemic  |
|  | and modulate expression of                 | lupus erythematosis, multiple          |
|  | immunomodulatory genes.                    | sclerosis and/or as described below)   |
|  | Exemplary assays for transcription         | and immunodeficiencies (e.g., as       |
|  | through the NFKB response element          | described below). Preferred            |
|  | that may be used or rountinely             | indications also include neoplastic    |
|  | modified to test NFKB-response             | diseases (e.g., leukemia, lymphoma,    |
|  | element activity of polypeptides of        | melanoma, and/or as described below    |
|  | the invention (including antibodies        | under "Hyperproliferative              |
|  | and agonists or antagonists of the         | Disorders"). Preferred indications     |
|  | invention) include assays disclosed in     | include neoplasms and cancer, such     |
|  | Berger et al., Gene 66:1-10 (1998);        | as, for example, leukemia,             |
|  | Cullen and Malm, Methods in                | lymphoma, melanoma, and prostate,      |
|  | Enzymol 216:362-368 (1992);                | breast, lung, colon, pancreatic,       |
|  | Henthorn et al., Proc Natl Acad Sci        | esophageal, stomach, brain, liver,     |
|  | USA 85:6342-6346 (1988); Stassen           | urinary tract cancers and as described |
|  | et al, J Immunol 166(7):4391-8             | below under "Hyperproliferative        |
|  | (2001); and Marquardt and Walker, J        | Disorders".                            |
|  | Allergy Clin Immunol 105(3):500-5          |                                        |
|  | (2000), the contents of each of which      |                                        |
|  | are herein incorporated by reference       |                                        |
|  | in its entirety. Mast cells that may be    |                                        |
|  | used according to these assays are         |                                        |
|  | publicly available (e.g., through the      |                                        |
|  | ATCC <sup>TM</sup> ). Exemplary human mast |                                        |
|  | cells that may be used according to        |                                        |
|  | these assays include the HMC-1 cell        |                                        |
|  | line, which is an immature human           |                                        |
|  | mast cell line established from the        |                                        |
|  | peripheral blood of a patient with         |                                        |
|  | mast cell leukemia, and exhibits           |                                        |
|  | many characteristics of immature           |                                        |
|  | mast cells.                                |                                        |

|    | HCUIIM65 | 445 | Production of VCAM     | Assays for measuring expression of    | Highly preferred indications include   |
|----|----------|-----|------------------------|---------------------------------------|----------------------------------------|
| 41 |          |     | in endothelial cells   | VCAM are well-known in the art and    | inflammation (acute and chronic).      |
|    |          |     | (such as human         | may be used or routinely modified to  | restnosis, atherosclerosis, asthma and |
|    |          |     | umbilical vein         | assess the ability of polypeptides of | allergy. Highly preferred indications  |
|    |          |     | endothelial cells      | the invention (including antibodies   | include inflammation and               |
|    |          |     | (HUVEC))               | and agonists or antagonists of the    | inflammatory disorders,                |
|    |          |     |                        | invention) to regulate VCAM           | immunological disorders, neoplastic    |
|    |          |     |                        | expression. For example, FMAT         | disorders (e.g. cancer/tumorigenesis), |
|    |          |     |                        | may be used to meaure the             | and cardiovascular disorders (such as  |
|    |          |     |                        | upregulation of cell surface VCAM-1   | described below under "Immune          |
|    |          |     |                        | expresssion in endothelial cells.     | Activity", "Blood-Related              |
|    |          |     |                        | Endothelial cells are cells that line | Disorders", "Hyperproliferative        |
|    |          |     |                        | blood vessels, and are involved in    | Disorders" and/or "Cardiovascular      |
|    |          |     |                        | functions that include, but are not   | Disorders"). Highly preferred          |
|    |          |     |                        | limited to, angiogenesis, vascular    | indications include neoplasms and      |
|    |          |     |                        | permeability, vascular tone, and      | cancers such as, for example,          |
|    |          |     |                        | immune cell extravasation.            | lcukemia, lymphoma, melanoma,          |
|    |          |     |                        | Exemplary endothelial cells that may  | renal cell carcinoma, and prostate,    |
|    |          |     |                        | be used according to these assays     | breast, lung, colon, pancreatic,       |
|    |          |     |                        | include human umbilical vein          | esophageal, stomach, brain, liver and  |
|    |          |     |                        | endothelial cells (HUVEC), which      | urinary cancer. Other preferred        |
|    |          |     |                        | are available from commercial         | indications include benign             |
|    |          |     |                        | sources. The expression of VCAM       | dysproliferative disorders and pre-    |
|    |          |     |                        | (CD106), a membrane-associated        | neoplastic conditions, such as, for    |
|    |          |     |                        | protein, can be upregulated by        | example, hyperplasia, metaplasia,      |
|    |          |     |                        | cytokines or other factors, and       | and/or dysplasia.                      |
|    |          |     |                        | contributes to the extravasation of   |                                        |
|    |          |     |                        | lymphocytes, leucocytes and other     |                                        |
|    |          |     |                        | immune cells from blood vessels;      |                                        |
|    |          |     |                        | thus VCAM expression plays a role     |                                        |
|    |          |     |                        | in promoting immune and               |                                        |
|    |          |     |                        | inflammatory responses.               |                                        |
|    | HCUIM65  | 445 | Activation of          | Assays for the activation of          | Highly preferred indications           |
| 14 |          |     | transcription through  | transcription through the Nuclear     | include blood disorders (e.g., as      |
|    |          |     | NFAT response          | Factor of Activated T cells (NFAT)    | described below under "Immune          |
|    |          |     | element in immune      | response element are well-known in    | Activity", "Blood-Related              |
|    |          |     | cells (such as natural | the art and may be used or routinely  | Disorders", and/or "Cardiovascular     |

| Disorders"). Highly preferred discussions in the disorders of the automimus diseases (e.g., rheumatoid arthmis, segment plus gestine tipnes experient plus e | whether and a second properties of a second p | include neophisms and enaceases, such the face ceample, lettlearning, lymphoma, and prostate breast, lung, soot, parceatted, seophingeal, asomach, brain, liver and untanay enear, Other preferred indications include benign dysproliferative discussions and preparative and preparation of the properties of the properties and pre-propletatic conditions, such as, for example, organized, superplasis metaplisis, and/or dysplasis. Preferred indications also include amenite, puncytopenia, theoperal, thrombo-yoperia, proception, and also include amenite, puncytopenia, Hodgin's disease, acute. Proposition and the proposition and ALL plasmacytomics multiple myelocha.                   |
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| modified to assess the ability of oppopendies of the irrention (including antibodies and agoniss or authorities of the irrention) for the irrention of the irrention of the irrention of regulate IVAT transcription factors and modifiate expression of genesi involved in immunomodulatory functions. Exemplary assys for transcription flungth the VRAT response element that may be used or municity modified to test IVAT response element that may be used or municity modified to test IVAT.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Oppophedics of the invention of including antibodies and agonists or mangenists of the invention) include asserts disclosed in Berger et al., Grate 66:1-10 (1998); Ollten and Manta, Methods in Enzymol 216:362-368 (1992); Hentlem et al., 216:362-368 (1992); Ambhint et al., 216:362-3 | Med 18(2)/8018 10 (1995); D.N. Med 18(2)/8018 10 (1995); D.N. Mere et al., Int. Discipling Cell Biol 31(10); 1231-1236 (1996); Fraser et al., 18 int. I fammalo 240/388844 (1999); and Yeseru et al., 18 flood P.M. 26(4): 12428-14235 (1994), the contents of each of which are breath of which are breath in proposately by reference in its entirety. Mc cells that may be taken in corporately by reference in its entirety. Mc cells that may be and excording to these assays are publicly available (e.g., through the ATCCP-b. Exemplary human NK ATCCP-b. Exemplary human NK and the assays and due the Mc and according to these assays and the third with the latter of the man parameter and the which is a fluor than a man and all effect cell line with cytolytic and cytotoxic cell line with cytolytic and cytotoxic |
| Killer cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|----|---------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------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| 14 | HCUIM65 | 445 | Activation of section of section of section in the section in the section in the section of section | transarription through the Serum<br>Response Ilement (SRE) are well-<br>Response Ilement (SRE) are well-<br>shown in the art and may be used or<br>routinely modified to assess the are<br>invention (including antibodies and the<br>invention (including antibodies and the<br>invention) to regulate so the<br>invention) to regulate so the<br>invention) to regulate sortun<br>response factors and modilate the<br>response factors and modilate the<br>growth and upogulate the function<br>growth and upogulate the function<br>(profession of genes involved in<br>growth and upogulate the function<br>to the service of the service of the service of the<br>service of the service of the service of the<br>profession of genes involved in<br>growth and upogulate the function<br>to the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the<br>service of the service of the service of the service of the service of the<br>service of the service of the<br>service of the service of | in vention in the preference dendeliment of the invention includes a method for inhibiting (e.g., recheing) TNF alpha production. An alternative highly preferred embediment of the preferred embediment of the simmlaring (e.g., increasing) TNF alpha production. Preferred mindications include blood disorders (e.g., as described below under Informations include blood disorders (e.g., as described below under Disorders), and/or "Cardiovascular Disorders", and/or "Cardiovascular Disorders", lattle option preferred indications include blood miscular include blood disorders (e.g., as described below under Disorders"). Blood below under Disorders, and/or "Cardiovascular Disorders", lattle preferred indications include autoimmune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| diseases (e.g., rhemmatoid arthritis,<br>segretin (tipus explematois);<br>Crohn's disease, multiple extensis,<br>andror as described below),<br>immunodeficiencies (e.g., as<br>described below), hosoling a Teell-<br>matelied immune response, and<br>supressing a T cell-mediated                                                                          | manner response. Acationian inginy preferred indications include and information and information and information and information and treating joint damage in southern seek and treating joint damage in southern seek and treating joint damage. An additional highly preferred indications include preferred indications include proposited cisasess (e.g., leukemin, lymphoma, and/or is described below under "lyperprohiticrative Dissorters"). Additionally, highly preferred indications include neoplisarus and cancers, such as, for mercanic, leukemin, lymphoma, melanoma, giotona (e.g., malignant melanoma, giotona (e.g., malignant breast, lung, coloto, pancretic), hereast, brang, coloto, pancretic), hereast, hung, coloto, pancretic hereast, hung coloto, pancretic hundrations and hereast hung conditions, so and pre-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | exampe, typeptasas, uteaptasas, and/or dysplasia. Preferred indications include anemia, pancyopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia |
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| transcription through the SRE that may be tased or untilingly modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or amagonists of the invention) include assiys (askesed in wrenton) include assiys (askesed in wrenton) include assiys (askesed in wrenton) Matha. Methods in Cullen and Malm, Methods in | The property of the property o |                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                |
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|   | A highly preferred indication is        | Assays for the regulation of          | Regulation of | 446 | HCWDS72 |  |
|---|-----------------------------------------|---------------------------------------|---------------|-----|---------|--|
|   | Disease and asthma and allerey          | _                                     |               |     |         |  |
|   | hypercoagulation, diabetes mellitus,    |                                       |               |     |         |  |
|   | tissues, hemophilia,                    |                                       |               |     |         |  |
|   | reactions to transplanted organs and    |                                       |               |     |         |  |
|   | psoriasis, suppression of immune        | _                                     |               |     |         |  |
|   | sepsis, neutropenia, neutrophilia,      |                                       |               |     |         |  |
|   | disease, inflammatory bowel disease,    |                                       |               |     |         |  |
|   | arthritis, AIDS, granulomatous          |                                       |               |     |         |  |
|   | plasmacytomas, multiple myeloma,        |                                       |               |     |         |  |
|   | lymphocytic anemia (ALL),               |                                       |               |     |         |  |
|   | thrombocytopenia, acute                 |                                       |               |     |         |  |
|   | pancytopenia, leukopenia,               |                                       |               |     |         |  |
|   | Preferred indications include anemia,   |                                       |               |     |         |  |
|   | idiopathic pulmonary fibrosis.          |                                       |               |     |         |  |
|   | additional preferred indication is      |                                       |               |     |         |  |
|   | infectious disease as described below   |                                       |               |     |         |  |
|   | malignant osteoporosis, and/or an       |                                       |               |     |         |  |
|   | granulomatosus disease and              |                                       |               |     |         |  |
|   | associated with chronic                 |                                       |               |     |         |  |
|   | infections, tuberculosis, infections    |                                       |               |     |         |  |
|   | Disorders"), and infection (e.g., viral | ATCC <sup>TM</sup> ).                 |               |     |         |  |
|   | Disorders", and/or "Cardiovascular      | publicly available (e.g., through the |               |     |         |  |
|   | "Immune Activity", "Blood-Related       | be used according to these assays are |               |     |         |  |
|   | (e.g., as described below under         | such as the SUPT cell line, that may  |               |     |         |  |
|   | indications include blood disorders     | entirety. Exemplary human T cells,    |               |     |         |  |
|   | disorders, Highly preferred             | incorporated by reference in its      |               |     |         |  |
|   | inflammation and inflammatory           | contents of each of which are herein  |               |     |         |  |
|   | inmune response. Additional             | Henttinen et al., J Immunol           |               |     |         |  |
|   | suppressing a T cell-mediated           | Blood 93(6):1980-1991 (1999); and     |               |     |         |  |
|   | mediated immune response, and           | 6346 (1988); Matikainen et al.,       |               |     |         |  |
|   | described below), boosting a T cell-    | Proc Natl Acad Sci USA 85:6342-       |               |     |         |  |
|   | helow), immunodeficiencies (e.g., as    | 216:362-368 (1992): Henthorn et al    |               |     |         |  |
| _ | multiple sclerosis and/or as described  | Malm Methods in Enzymol               |               |     |         |  |
|   |                                         |                                       |               |     |         |  |

| o dishotos mallitus         | additional highly preferred |                        | diabetes (e.g., diabetic retinopathy, | nd diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy |                                         | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | <ol> <li>(e.g., due to diabetic neuropathy),</li> </ol> | t blood vessel blockage, heart disease, |                                 | PAR   diabetic neuropathy or blood vessel | r   blockage), seizures, mental | Ť                                  | hyperglycenic-hyperosmolar coma, | Ť                                    | Ť                                  | _                                 | _                                   | Ť                                   |                                | _                                   | Ť                               | <ol> <li>"Endocrine Disorders" section</li> </ol> |                                 |                                  | and blindness), ulcers and impaired | wound healing, and infection (e.g., |                                     | described in the "Infectious | <ol> <li>Diseases" section below, especially</li> </ol> | n of the urinary tract and skin), carpal | he unnel syndrome and Dupuytren's | in   contracture). An additional    |   |
|-----------------------------|-----------------------------|------------------------|---------------------------------------|-----------------------------------------|-----------------------------------|-----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|---------------------------------------------------------|-----------------------------------------|---------------------------------|-------------------------------------------|---------------------------------|------------------------------------|----------------------------------|--------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|--------------------------------|-------------------------------------|---------------------------------|---------------------------------------------------|---------------------------------|----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|------------------------------|---------------------------------------------------------|------------------------------------------|-----------------------------------|-------------------------------------|---|
| termination of Matio Engage |                             | Ť                      | the ability of polypeptides of the    | invention (including antibodies and     | agonists or antagonists of the    | invention) to regulate transcription of | Malic Enzyme, a key enzyme in      | lipogenesis. Malic enzyme is         | involved in lipogenesisand its | expression is stimulted by insulin.                     | ME promoter contains two direct         | repeat (DR1)- like elements MEp | and MEd identified as putative PPAR       | response elements. ME promoter  | may also responds to AP1 and other | transcription factors. Exemplary | assays that may be used or routinely | modified to test for regulation of | transcription of Malic Enzyme (in | adipoocytes) by polypeptides of the | invention (including antibodies and | agonists or antagonists of the | invention) include assays disclosed | in: Streeper, R.S., et al., Mol | Endocrinol, 12(11):1778-91 (1998);                | Garcia-Jimenez, C., et al., Mol | Endocrinol, 8(10):1361-9 (1994); | Barroso, I., et al., J Biol Chem,   | 274(25):17997-8004 (1999);          | ljpenberg, A., et al., J Biol Chem, | 272(32):20108-20117 (1997);  | Berger, et al., Gene 66:1-10 (1988);                    | and, Cullen, B., et al., Methods in      | Enzymol. 216:362-368 (1992), the  | contents of each of which is herein |   |
| of Marianisation of Malic   | Enzyme in adinocytes        | and for the same forms |                                       |                                         |                                   |                                         |                                    |                                      |                                |                                                         |                                         |                                 |                                           |                                 |                                    |                                  |                                      |                                    |                                   |                                     |                                     |                                |                                     |                                 |                                                   |                                 |                                  |                                     |                                     |                                     |                              |                                                         |                                          |                                   |                                     |   |
| 43                          |                             |                        |                                       |                                         |                                   |                                         |                                    |                                      |                                |                                                         |                                         |                                 |                                           |                                 |                                    |                                  |                                      |                                    |                                   |                                     |                                     |                                |                                     |                                 |                                                   |                                 |                                  |                                     |                                     |                                     |                              |                                                         |                                          |                                   |                                     | _ |

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Hepatocytes that may be and act decording to these assays are publicly available (e.g., through the CACC'V) and/ver may be routinely generated. Exemplary bepatocytes that may be used according to these assays includes the HHIE rat liver bepatoms cell line.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | and/or complications associated with<br>observed and in the preferred<br>indications include weight loss or<br>alternatively, weight gain. Additional lightly preferred<br>indications are complications<br>associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <del>.</del> | HCWKCIS | 447 | transcription of transc | transcription through the DMET transcription through the DMET response element are well-known in medical or a rand may be used or noutacyl modified to assess the ability of polyperdises of the invention of including anthodies and agonisis or anatomists of the invention) to activate the DMET response element in a report construct each as that containing the GLUT4 the assistance of the compared of the containing the GLUT4 as that containing the GLUT4 as that containing the GLUT4 through the containing the GLUT4 transcription factor and another for resulting its services and its decled muscle.  GLUT4 is the primary insulin- research transcription factor and another transcription factor a | highly proferred inflexion is judicy acquired inflexion lightly precident inflexion lightly precident inflexions include to profilexing seasonized with dialoctes (e.g., diabetic reintopathy, kithey disease (e.g., renal failure, hephropathy and read or other diseases and diseators as and diseators in earth of the companion of th |
|              |         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and agonists or aniagonists of the<br>invention) include assays disclosed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | below), neuropathy, vision<br>impairment (e.g., diabetic retinopathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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|         |     |                                                                                  | Thirli, M.V., et al. J Biol Chen, Trilla, M.V., et al. J Biol Chen, and a strain a strain a strain a strain and a strain and a strain a strain a strain a strain a strain and a strain a strain a strain and a strain and a strain and a strain and a strain a strain and a strain a | wound healing, and infection (e.g., wound healing, and infection (e.g., activations diseased and disorders as described in the "Infections accessed and disorders as described in the "Infections accessed section below, especially of the urimary tract and skii). An additional heality preferred indications is obesity and/e complications associated with obesity. Additional weight loss or alternatively, weight weight loss or alternatively, weight weight loss or alternatively, weight weight loss or alternatively. Weight weight loss or alternatively weight indications are complications associated with instilin resistance. |
|---------|-----|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HCWKC15 | 447 | Activation of<br>transcription through<br>cAMP response<br>clement (CRE) in pre- | Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|         |     | adipocytes.                                                                      | modified to assess the ability of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | weight loss or alternatively, weight                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| preferred indications are<br>complications associated with insulin<br>resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | helphy pretreet and indication is obesity and/or complications is about a contribution of the properties of the properti |
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| and/or may be routinely generated.  Exemplar mouse adhocyte cells that may be used according to these seasys include 712-1 cells 317-1.1 is an adherent mouse preading-oye cell line that is a continuous substrain of 3173 fibroblas cells developed through cleand isolation and undergo through cleand isolation and undergo conversion under appropriate conversion under appropriate the conversion und | transcription through the Scum Resones Element (SRB) are well- known in the art and may be used or known in the art and may be used or minely medified to assess the ability of polypeptides of the ability of polypeptides of the mirrorino (including antibodics and agonists or maganists of the invention) to regulate the serum response factors and modulate the copression of genes involved in growth. Exemplacy assays for transcription through the SRB that measurption through the SRB that transcription through the SRB that the service and agonists or antigonists to the transcription through the SRB that the production of the polypeptides and agonists or antigonists to the transcription through the SRB that the transcription through the service of the transcription through the SRB that the transcription through the service through the transcription through th |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transcription through secretarities of transcription through serum response element in pre-adiposytes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| microvascular disease, hypertension, aske, and other diseases and diseases and diseases and diseases and diseases are described in the claimons and asked of the disease section below), despindenta, endecrine disearders (se described in the failedorm Disease (se described in the below), the disearders (se described in the below), the disearcher section below), trempatify, vision below), trempatify, vision below), trempatify, vision below), trempatify, vision below). | injunitrunt (e.g., chibetic retinoputhy<br>and blindness), dieters and impaired<br>burnd healing, and infection (e.g.,<br>infections diseases and disorders as<br>described in the 'Infections'<br>burnsess' section below). Additional<br>highly preferred indications are<br>complications associated with insulin<br>resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | aschan, allely precented indications include aschan, allelegy, hypersensitivity reactions, inflammator) deathers. Additional highly preferred indications include manner and hermoposite disorders (e.g., as described below under Humanne Anderson), and "Blood-Rechard Disorders"), and "Blood-Rechard Disorders", and "Blood-Rechard Disorders", and "Blood-Rechard Disorders"), nurmanofediciencies (e.g., as described below), immunofediciencies (e.g., as described below). In obsuing an ocosinophil-mediated immune response.                                                                                                                                                                  |
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| which are herein incorporated by effective in its attricty. Pre- adipocytes that may be used a coording to these uses as see publicly available (e.g., through the ATCCPA) and or may be routinely generated. Are extra pire mouse a athory to exist so that may be used as a through or less than may be used as a through or less than may be used as ordinely generated.                                                                                                           | is an adherent mouse practition, 513-LI, eds. 513-LI, eds | transacription through the Gamma Interferon Activation of Interferon Activation Sile (GAS) assource element are well-known in the art and may be used or routinely modified to assess the ability of polypspixies of the invention of including ampleids and agoinsts or autagonists of the invention) to managonists of the invention) to modified gene expression (commonly via STAT mascription and autagonists of the invention) to managonists of the invention of commonly via STAT mascription and page and the activity of reasserption through the CAS, are passed selement and through the CAS, are passed selement and through the CAS, approached charm activity of polypepticles of the invention including amploids and agonists or distribution amploids and agonists or distribution and polyperoptics of the invention including amploids including amploids including amploids and agonists or distribution amploids. |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| 4 | assays disclosed in Berger et al., | Malm. Methods in Enzymol | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Matikainen et al., | Blood 93(6):1980-1991 (1999); and | Henttinen et al., J Immunol | 155(10):4582-4587 (1995); the | contents of each of which are herein | incorporated by reference in its | entirety. Moreover, exemplary | assays that may be used or routinely | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to | activate or inhibit activation of | immune cells include assays | disclosed and/or cited in: Mayumi | M., "EoL-1, a human eosinophilic | cell line" Leuk Lymphoma; | Jun;7(3):243-50 (1992); | Bhattacharya S, "Granulocyte | macrophage colony-stimulating | factor and interleukin-5 activate | STAT5 and induce CIS1 mRNA in | human peripheral blood eosinophils" | Am J Respir Cell Mol Biol; | Mar;24(3):312-6 (2001); and, Du J, | et al., "Engagement of the CrkL | adapter in interleukin-5 signaling in | eosinophils" J Biol Chem; Oct | 20;275(42):33167-75 (2000); the | contents of each of which are herein | incorporated by reference in its | entirety. Exemplary cells that may |
|---|------------------------------------|--------------------------|--------------------------------------|---------------------------------|---------------------------------|-----------------------------------|-----------------------------|-------------------------------|--------------------------------------|----------------------------------|-------------------------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|----------------------------------|-----------------------------------|-----------------------------|-----------------------------------|----------------------------------|---------------------------|-------------------------|------------------------------|-------------------------------|-----------------------------------|-------------------------------|-------------------------------------|----------------------------|------------------------------------|---------------------------------|---------------------------------------|-------------------------------|---------------------------------|--------------------------------------|----------------------------------|------------------------------------|
|   |                                    |                          |                                      |                                 |                                 |                                   |                             |                               |                                      |                                  |                               |                                      |                                   |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                               |                                     |                            |                                    |                                 |                                       |                               |                                 |                                      |                                  |                                    |
|   |                                    |                          |                                      |                                 |                                 |                                   |                             |                               |                                      |                                  |                               |                                      |                                   |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                               |                                     |                            |                                    |                                 |                                       |                               |                                 |                                      |                                  |                                    |

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| and against a continuo degragates of a limamon degragates of a LEA plot (1997), Arambana et al., LEA plot (1997), Arambana et al., LEA plot (1997), Arambana et al., LEA plot (1997), the contents of each of which are where innoprotuced by reference in its entirely. For example, a supervise segment is entirely. For example, a increases in transcription inducible in content in a propossive element in EOL-1 cells) may link the NIKB increases in transcription factor, and NEB transcription factor, and the NIKB transcription factor, and the supervise element in a reporter gare and binds to the NIKB transcription factor, and other factors. Examplar and other factors. Examplar and other factors. Examplar conting to these assays include evoluting in the alleggic responses; they are recruited to important in the alleggic responses; they are recruited to responses of that stage allerging ellergic responses of that stage allerging ellerging ellergic ellerging for the stage allerging and evolution for the transcrip. Foll-lis is human evolutionally in the allerging ellerging allerging allergin | This reporter asset measures activation of the GATA-3 signating pathway in HMC-1 human mass cell line. Activation of GATA-3 in mast cells has been linical to spoistine and the memokine production. Assays for the activation of transcription the activation of transcription the activation of transcription cleaners are well-known in the art and may be used or routinely productively or assays he ability of modified to assays he ability of               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of transcription through CATA-5 response element in immune cells (such as mast cells).                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Disorders", and/or "Cardiovascular | Disorders"). Preferred indications    | include autoimmune diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis    | and/or as described below) and      | immunodeficiencies (e.g., as      | described below). Preferred     | indications include neoplastic       | discases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary    | tract cancers and/or as described     | below under "Hyperproliferative    | Disorders"). Other preferred    | indications include benign | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | thrombocytopenia, leukemias,       | Hodgkin's disease, acute            | lymphocytic anemia (ALL),           | plasmacytomas, multiple myeloma,     | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, sepsis, neutropenia,   | neutrophilia, psoriasis, suppression   | of immune reactions to transplanted | organs and tissues, hemophilia,            | hypercoagulation, diabetes mellitus, | endocarditis, meningitis, and Lyme  | Disease.                         |                                     |
|------------------------------------|---------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------------|--------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|
| polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to   | regulate GATA3 transcription factors | and modulate expression of mast cell | genes important for immune response | development. Exemplary assays for | transcription through the GATA3 | response element that may be used or | routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its    | entirety. Mast cells that may be used | according to these assays are publicly | available (c.g., through the        | ATCC <sup>TM</sup> ). Exemplary human mast | cells that may be used according to  | these assays include the HMC-1 cell | line, which is an immature human | mast cell line established from the |
|                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |
| _                                  |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |

|                                                                                                                  | Highly preferred indications include allegy, all preferred indications include allegy, all preferred indications include animalitie is specified include animalitie is specified include animalitie is specified include animalitie is specified include include animalitie is specified below). Preferred include includential arthrities specified below) and diseasing include including |
|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells. | activation of the NHAT signaling pathway in Reporter super interaction of the NHAT signaling pathway in HMC-1 human must cell human and cell human and red human of the NHAT luman such substance of the NHAT luman such substantial of the substantial of the substantial of the activation of transcription for the activation of transcription for the activation of transcription for the activation of transcription in the art and may be used or routinely of polyperplaces of the invention) to polyperplaces of the invention) to antiquorists of the invention factors and modaline expression of geness in modaline expression of geness of modaline expression of genes of invitations. Exemplary assays for transcription through the NHAT response element attituty of the invention includes madige the or less than antipolysed and agonists or antipolysed activity of the invention includes assays disclosed in Berger et al. Case Cel. 10 (1922). Herborn et al., pp. 20. 156. 32. 568 (1922). Herborn et al., pp. Proc. Net al. 20. 17. 17. 17. 17.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                  | Activation of a constraint of transcription through through through the NFAT response chieses in immune cells (such as must cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                  | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                  | HCWKC15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| pancytopetia, letkopenia, inchenias, inchenias, inchenias, inchedias, letkenias, inchenias, inchecongulation, directes millines, endocendris, meninglis, and Lyme Disease.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | allegy, seitum, and rhimin, allegy, method and rhimin, allegy, saltum, and rhimin, and rhimin, allegy, seitum, and rhimin, and rhimin, and additional lightly referred indecine (e.g., an indicentions include infection (e.g., an indimumation and inflammation and searched below under "Immune Observies"). Preferred inflammation Boarders'). Preferred inflammation and arthritis, systemic Open and all the properties and an individual and arthritis, systemic e.g., rheumanid arthritis, systemic secrets and or set described below.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| 164(1979); Ali et al., I Immunol 164(1971); Ali et al., I Immunol 164(197712); Ali 2000; Huddhison and McG-taska, J Biol Menra 20(42); Ali 234-16539 (1959), and Tumer et al., 15-p Med al. Market et al., 15-p Med | in sporter space unesages activation of the NFBS ignating the photory in MEV. In human mast cell line, Activation of NFBB immast cell line, Activation of NFBB im mast certain cytokiens, such as IL-6 and the properties of the activation of transcripton intrough the NFBB response centent are well-known in transcripton intrough the NFBB response centent are well-known in modified to assess the ability of propeptides of the invention (including antibodies and agonists or amagonists of the invention) to regulate NFBB invascription faces and ondulate cepessistion of automational conference of the control of the control of the invention to regulate NFBB invascription faces and modulate cepessistion of intrammomodulatory series.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | transcription through a<br>Activation of<br>Activation |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HCWKCIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|   |         |     |                                      | mast cell leukemia, and exhibits<br>many characteristics of immature<br>mast cells. | endocarditis, meningitis, and Lyme<br>Disease.            |
|---|---------|-----|--------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|
| ç | HCWKC15 | 447 | Activation of                        | This reporter assay measures                                                        | Highly preferred indication includes                      |
| 5 |         |     | ranscription unough<br>NFKB response | activation of the linkin signating<br>pathway in Ku812 human basophil               | anergy, astrina, and rimitis. Additional highly preferred |
|   |         |     | element in immune                    | cell line. Assays for the activation of                                             | indications include infection (e.g., an                   |
|   |         |     | cells (such as                       | transcription through the NFKB                                                      | infectious disease as described below                     |
|   |         |     | basophils).                          | response element are well-known in                                                  | under "Infectious Disease"), and                          |
|   |         |     |                                      | the art and may be used or routinely                                                | inflammation and inflammatory                             |
|   |         |     |                                      | modified to assess the ability of                                                   | disorders. Preferred indications                          |
|   |         |     |                                      | polypeptides of the invention                                                       | include immunological and                                 |
|   |         |     |                                      | (including antibodies and agonists or                                               | hempatopoietic disorders (e.g., as                        |
|   |         |     |                                      | antagonists of the invention) to                                                    | described below under "Immune                             |
|   |         |     |                                      | regulate NFKB transcription factors                                                 | Activity", and "Blood-Related                             |
|   |         |     |                                      | and modulate expression of                                                          | Disorders"). Preferred indications                        |
|   |         |     |                                      | immunomodulatory genes.                                                             | also include autoimmune diseases                          |
|   |         |     |                                      | Exemplary assays for transcription                                                  | (e.g., rheumatoid arthritis, systemic                     |
|   |         |     |                                      | through the NFKB response element                                                   | lupus erythematosis, multiple                             |
|   |         |     |                                      | that may be used or rountinely                                                      | sclerosis and/or as described below)                      |
|   |         |     |                                      | modified to test NFKB-response                                                      | and immunodeficiencies (e.g., as                          |
|   |         |     |                                      | element activity of polypeptides of                                                 | described below). Preferred                               |
|   |         |     |                                      | the invention (including antibodies                                                 | indications also include neoplastic                       |
|   |         |     |                                      | and agonists or antagonists of the                                                  | diseases (e.g., leukemia, lymphoma,                       |
|   |         |     |                                      | invention) include assays disclosed in                                              | melanoma, and/or as described below                       |
|   |         |     |                                      | Berger et al., Gene 66:1-10 (1998);                                                 | under "Hyperproliferative                                 |
|   |         |     |                                      | Cullen and Malm, Methods in                                                         | Disorders"). Preferred indications                        |
|   |         |     |                                      | Enzymol 216:362-368 (1992);                                                         | include neoplasms and cancer, such                        |
|   |         |     |                                      | Henthorn et al., Proc Natl Acad Sci                                                 | as, for example, leukemia,                                |
|   |         |     |                                      | USA 85:6342-6346 (1988); Marone                                                     | lymphoma, melanoma, and prostate,                         |
|   |         |     |                                      | et al, Int Arch Allergy Immunol                                                     | breast, lung, colon, pancreatic,                          |
|   |         |     |                                      | 114(3):207-17 (1997), the contents of                                               | esophageal, stomach, brain, liver,                        |
|   |         |     |                                      | each of which are herein                                                            | urinary tract cancers and as described                    |
|   |         |     |                                      | incorporated by reference in its                                                    | below under "Hyperproliferative                           |
|   |         |     |                                      | entirety. Basophils that may be used                                                | Disorders".                                               |
|   |         |     |                                      | according to these assays are publicly                                              |                                                           |
|   |         |     |                                      | available (e.g., through the                                                        |                                                           |

| le l                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Highly percent inclusions  AT)  described below under "Immune ready Disorders, "andor "Cardiovacular ready Disorders," andor "Cardiovacular ready Disorders, "andor "Cardiovacular ready process ready and ready season (p. "Learnando dirritis, systemic limpus erythemunesis, multiple selectors and or as described below), immune response, and emittiple selectors, besoning a T cell-mediated ready processe and a T cell-mediated or ready and the processes, and excepted below, boosing a T cell- mediated immune response, and emitting a for the ready of th |
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| hardrown hardrown beautiful beautifu | sayes for the activation of rasseys for the activation of transcription through the Nuclear Factes of Activated T cells (NFAT) response element are well-known in the art and may be used or noutinely under the activation of the activation of the activation of polypoptides of the invention in causing management of probypoptides of the invention in causing management of a management of the invention in central for polypoptides of the invention of polypoptides of the invention of polypoptides of the invention in challeng and management activity of polypoptides of the invention in challeng and the invention in challeng and the invention in the Gene 66:1-10 (1998), Cultien and Manin, Methods and agent its Enzymon 216:362-386 (1992); Henthour et al., 1785 (1998); Andrew et al., 1785 (1998); Andrew et al., 1785 (1998); Deser et al. 118 (1998); The Berer et  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Advisation of Advisation of transacription through NPAT response clearest it immune celts (such as natural Riller cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCWKC15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| lymphorma, and prostate, breast, lung- soumach, Partin, Iter and utnary summeth, Partin, Iter and utnary accor, Chep preferred indications include benign dysproliferative disorders and pre-couplastic conditions, such as, for example, hyperplasia, metaplasia, and or hyperplasia, predicted indications also include aromin, puncytopania, proportin, predicted indications also include aromin, puncytopania, flodgária disease, acute florigati, lumbinocytopania, indigária disease, such florigati, lumbinocytopania, arbitis, AIDS, granulorianous disease, inflammatory metaplinia, psoriasis, suppression organs and tissus, benophillia, hypercoogalantion, diaches mellinis, hypercoogalantion, diaches mellinis, hypercoogalantion, diaches mellinis, hypercoogalantion, diaches mellinis, bysecondalis, ammingiis, tyme Diseases, safirma and allergy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Inglity prefere indeations include inflammatory disorders. Highly preferred indeations shade bound also described in the control of the contr |
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| 31(10):1221-1236 (1999); Fraser et al., item faired in and vescen et al., 1810 (1999); and Yesser et al., 1810 (1999); and Yesser et al., 1810 (1990); and Yesser et al., 1810 (1991); and Yesser et al., 1810 (1992); and Yes | assays for the activation of transacription through the VRKB response element are well-known in the art and may be used or nouties) modified to assess the ability of hoppspendise of the invention of including antibodies and agonists or expension of regulate VRKB transcription factors and modulate expression of immunomodificatory genes. Exemplary assays for transcription factors invention and modulate expression of Exemplary assays for transcription factors inventibate assays for transcription factors and modulate expression of Exemplary assays for transcription factors inventibate and properties of the activation of the activ |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transarijoto drough<br>WRGI response<br>colis (such as natural<br>Killer cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCWKCIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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|    | HCWKC15 | 447 | Activation of             | Assavs for the activation of           | A preferred embodiment of the          |
|----|---------|-----|---------------------------|----------------------------------------|----------------------------------------|
| 43 |         |     | transcription through     | transcription through the Serum        | invention includes a method for        |
|    |         |     | serum response element    | Response Element (SRE) are well-       | inhibiting (e.g., reducing) TNF alpha  |
|    |         |     | in immune cells (such     | known in the art and may be used or    | production. An alternative highly      |
|    |         |     | as natural killer cells). | routinely modified to assess the       | preferred embodiment of the            |
|    |         |     |                           | ability of polypeptides of the         | invention includes a method for        |
|    |         |     |                           | invention (including antibodies and    | stimulating (e.g., increasing) TNF     |
|    |         |     |                           | agonists or antagonists of the         | alpha production. Preferred            |
|    |         |     |                           | invention) to regulate serum           | indications include blood disorders    |
|    |         |     |                           | response factors and modulate the      | (e.g., as described below under        |
|    |         |     |                           | expression of genes involved in        | "Immune Activity", "Blood-Related      |
|    |         |     |                           | growth and upregulate the function     | Disorders", and/or "Cardiovascular     |
|    |         |     |                           | of growth-related genes in many cell   | Disorders"), Highly preferred          |
|    |         |     |                           | types. Exemplary assays for            | indications include autoimmune         |
|    |         |     |                           | transcription through the SRE that     | diseases (e.g., rheumatoid arthritis,  |
|    |         |     |                           | may be used or routinely modified to   | systemic lupus erythematosis,          |
|    |         |     |                           | test SRE activity of the polypeptides  | Crohn"s disease, multiple sclerosis    |
|    |         |     |                           | of the invention (including antibodies | and/or as described below),            |
|    |         |     |                           | and agonists or antagonists of the     | immunodeficiencies (e.g., as           |
|    |         |     |                           | invention) include assays disclosed in | described below), boosting a T cell-   |
|    |         |     |                           | Berger et al., Gene 66:1-10 (1998);    | mediated immune response, and          |
|    |         |     |                           | Cullen and Malm, Methods in            | suppressing a T cell-mediated          |
|    |         |     |                           | Enzymol 216:362-368 (1992);            | immune response. Additional highly     |
|    |         |     |                           | Henthorn et al., Proc Natl Acad Sci    | preferred indications include          |
|    |         |     |                           | USA 85:6342-6346 (1988); Benson        | inflammation and inflammatory          |
|    |         |     |                           | et al., J Immunol 153(9):3862-3873     | disorders, and treating joint damage   |
|    |         |     |                           | (1994); and Black et al., Virus Genes  | in patients with rheumatoid arthritis. |
|    |         |     |                           | 12(2):105-117 (1997), the content of   | An additional highly preferred         |
|    |         |     |                           | each of which are herein               | indication is sepsis. Highly           |
|    |         |     |                           | incorporated by reference in its       | preferred indications include          |
|    |         |     |                           | entirety. T cells that may be used     | neoplastic diseases (e.g., leukemia,   |
|    |         |     |                           | according to these assays are publicly | lymphoma, and/or as described          |
|    |         |     |                           | available (e.g., through the           | below under "Hyperproliferative        |
|    |         |     |                           | ATCCTM). Exemplary T cells that        | Disorders"). Additionally, highly      |
|    |         |     |                           | may be used according to these         | preferred indications include          |
|    |         |     |                           | assays include the NK-YT cell line,    | neoplasms and cancers, such as, for    |
|    |         |     |                           | which is a human natural killer cell   | example, leukemia, lymphoma,           |

|    |         |     |                        | line with extolytic and extotoxic     | melanoma olioma (e o malionant        |
|----|---------|-----|------------------------|---------------------------------------|---------------------------------------|
|    |         |     |                        | activity.                             | glioma), solid timors, and prostate.  |
|    |         |     |                        | . 6.                                  | breast, lung, colon, pancreatic,      |
|    |         |     |                        |                                       | esophageal, stomach, brain, liver and |
|    |         |     |                        |                                       | urinary cancer. Other preferred       |
|    |         |     |                        |                                       | indications include benign            |
|    |         |     |                        |                                       | dysproliferative disorders and pre-   |
|    |         |     |                        |                                       | neoplastic conditions, such as, for   |
|    |         |     |                        |                                       | example, hyperplasia, metaplasia,     |
|    |         |     |                        |                                       | and/or dysplasia. Preferred           |
|    |         |     |                        |                                       | indications include anemia,           |
|    |         |     |                        |                                       | pancytopenia, leukopenia,             |
|    |         |     |                        |                                       | thrombocytopenia, Hodgkin's           |
|    |         |     |                        |                                       | disease, acute lymphocytic anemia     |
|    |         |     |                        |                                       | (ALL), plasmacytomas, multiple        |
|    |         |     |                        |                                       | myeloma, Burkitt's lymphoma,          |
|    |         |     |                        |                                       | arthritis, AIDS, granulomatous        |
|    |         |     |                        |                                       | disease, inflammatory bowel disease,  |
|    |         |     |                        |                                       | neutropenia, neutrophilia, psoriasis, |
|    |         |     |                        |                                       | suppression of immune reactions to    |
|    |         |     |                        |                                       | transplanted organs and tissues,      |
|    |         |     |                        |                                       | hemophilia, hypercoagulation,         |
|    |         |     |                        |                                       | diabetes mellitus, endocarditis,      |
|    |         |     |                        |                                       | meningitis, Lyme Disease, cardiac     |
|    |         |     |                        |                                       | reperfusion injury, and asthma and    |
|    |         |     |                        |                                       | allergy. An additional preferred      |
|    |         |     |                        |                                       | indication is infection (e.g., an     |
|    |         |     |                        |                                       | infectious disease as described below |
|    |         |     |                        |                                       | under "Infectious Disease").          |
|    | HCWKC15 | 447 | Activation of          | Assays for the activation of          | Highly preferred indications          |
| 43 |         |     | transcription through  | transcription through the NFKB        | include inflammation and              |
|    |         |     | NFKB response          | response element are well-known in    | inflammatory disorders. Highly        |
|    |         |     | element in immune      | the art and may be used or routinely  | preferred indications include blood   |
|    |         |     | cells (such as natural | modified to assess the ability of     | disorders (e.g., as described below   |
|    |         |     | killer cells).         | polypeptides of the invention         | under "Immune Activity", "Blood-      |
|    |         |     |                        | (including antibodies and agonists or | Related Disorders", and/or            |
|    |         |     |                        | antagonists of the invention) to      | "Cardiovascular Disorders"). Highly   |

| preferred indications include       | autommune diseases (e.g.,<br>rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis  | and/or as described below), and   | immunodeficiencies (e.g., as   | described below). An additional | highly preferred indication is      | infection (e.g., AIDS, and/or an    | infectious disease as described below | under "Infectious Disease").           | Highly preferred indications include | neoplastic diseases (e.g., melanoma, | leukemia, lymphoma, and/or as | described below under               | "Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as, for | example, melanoma, renal cell        | carcinoma, leukemia, lymphoma, and | prostate, breast, lung, colon,        | pancreatic, esophageal, stomach,     | orain, liver and urinary cancer. Other | preferred indications include benign | dysproliferative disorders and pre-   | neoplastic conditions, such as, for      | example, hyperplasia, metaplasia,   | and/or dysplasia. Preferred       | indications also include anemia,      | pancytopenia, leukopenia,      | hrombocytopenia, Hodgkin's         | discase, acute lymphocytic anemia    | (ALL), plasmacytomas, multiple | myeloma, Burkitt's lymphoma,       | arthritis, AIDS, granulomatous  | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, |
|-------------------------------------|-------------------------------------------------------------------|------------------------------------|-----------------------------------|--------------------------------|---------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|------------------------------------|---------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|---------------------------------------|------------------------------------------|-------------------------------------|-----------------------------------|---------------------------------------|--------------------------------|------------------------------------|--------------------------------------|--------------------------------|------------------------------------|---------------------------------|--------------------------------------|------------------------------------|
| regulate NFKB transcription factors | and modulate expression of<br>immunomodulatory genes.             | Exemplary assays for transcription | through the NFKB response element | that may be used or rountinely | modified to test NFKB-response  | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the    | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998);  | Cullen and Malm, Methods in          | Enzymol 216:362-368 (1992);   | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Valle   | Blazquez et al, Immunology           | 90(3):455-460 (1997); Aramburau et  | al., J Exp Med 82(3):801-810 (1995); | and Fraser et al., 29(3):838-844   | (1999), the contents of each of which | are herein incorporated by reference | in its entirety. NK cells that may be  | used according to these assays are   | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary human NK | cells that may be used according to | these assays include the NKL cell | line, which is a human natural killer | cell line established from the | peripheral blood of a patient with | large granular lymphocytic leukemia. | This IL-2 dependent suspension | culture cell line has a morphology | resembling that of activated NK | cells.                               |                                    |
|                                     |                                                                   |                                    |                                   |                                |                                 |                                     |                                     |                                       |                                        |                                      |                                      |                               |                                     |                                  |                                      |                                     |                                      |                                    |                                       |                                      |                                        |                                      |                                       |                                          |                                     |                                   |                                       |                                |                                    |                                      |                                |                                    |                                 |                                      |                                    |
|                                     |                                                                   |                                    |                                   |                                |                                 |                                     |                                     |                                       |                                        |                                      |                                      |                               |                                     |                                  |                                      |                                     |                                      |                                    |                                       |                                      |                                        |                                      |                                       |                                          |                                     |                                   |                                       |                                |                                    |                                      |                                |                                    |                                 |                                      |                                    |
|                                     |                                                                   |                                    |                                   |                                |                                 |                                     |                                     |                                       |                                        |                                      |                                      |                               |                                     |                                  |                                      |                                     |                                      |                                    |                                       |                                      |                                        |                                      |                                       |                                          |                                     |                                   |                                       |                                |                                    |                                      |                                |                                    |                                 |                                      |                                    |

| production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune hissasses (or phenometaria) arthritis                                                               | systemic lipus erythermiosis,<br>systemic lipus erythermiosis,<br>sumitipe selectors and/or as described<br>below), immunodeliciencis (e.g., as<br>executed below), bosting a T cell-<br>mediated immune response, and<br>suppressing a T cell-mediated<br>suppressing a T cell-mediated<br>primature response. It flighty<br>preferred indications include                                                              | roughsist desaces (e.g., melinoma, renal cell carcinoma, leukema, luphinoma, and rough or a desarbed below under "Hyperprolificative below under "Hyperprolificative indicatives include nonplasms and canaces, such as for example, melinoma (e.g., measatic melinoma), e.g., measatic melinoma, ye.an et el carcinoma example, tend tell carcinoma example. | breast, ling, colon, panceratic, colon, panceratic, colon, panceratic, colon, panceratic, colon, panceratic, colon, panceratic, colongeals, stomach, brain, liver and univary cancer. Other preferred indications include benign indications include benign morphistic conditions, such as, for neoplastic conditions, such as, for morphistic conditions, such as, for morphistic conditions, such as, for expension, by preferred indication includes and or dysplassia. A highly perferred indication includes indication such allows and colonial such as a part of the pa |
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| USA 85:6342-6346 (1988); McGuire and lacebell; J Immunol and lacebell; J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):459-560 (1008); h.Biol Chem 3(1):459-560 (1008); h.Biol | equation (1994), and extended and extended and extended and extended in its entirety. Tells that may be used extended in the cutturety. Tells that may be used available (e.g., through the ATCUN). Exemplary human T cells that may be used according to these assets are publicly available (e.g., through the ATCUN). Exemplary human T cells that may be used according to these assets sincline the SUPT cell line. | which is a suspension culture of IL-2<br>and IL-4 responsive T cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|         |     |                       |                                       | gramilomatous disease, and           |
|---------|-----|-----------------------|---------------------------------------|--------------------------------------|
|         |     |                       |                                       | osteonorosis and/or as described     |
|         |     |                       |                                       | below under "Infectious Disease").   |
|         |     |                       |                                       | A highly preferred indication is     |
|         |     |                       |                                       | AIDS. Additional highly preferred    |
|         |     |                       |                                       | indications include suppression of   |
|         |     |                       |                                       | immune reactions to transplanted     |
|         |     |                       |                                       | organs and/or tissues, uveitis,      |
|         |     |                       |                                       | psoriasis, and tropical spastic      |
|         |     |                       |                                       | paraparesis. Preferred indications   |
|         |     |                       |                                       | include blood disorders (e.g., as    |
|         |     |                       |                                       | described below under "Immune        |
|         |     |                       |                                       | Activity", "Blood-Related            |
|         |     |                       |                                       | Disorders", and/or "Cardiovascular   |
|         |     |                       |                                       | Disorders"). Preferred indications   |
|         |     |                       |                                       | also include anemia, pancytopenia,   |
|         |     |                       |                                       | leukopenia, thrombocytopenia,        |
|         |     |                       |                                       | Hodgkin's disease, acute             |
|         |     |                       |                                       | lymphocytic anemia (ALL),            |
|         |     |                       |                                       | plasmacytomas, multiple myeloma,     |
|         |     |                       |                                       | Burkitt's lymphoma, arthritis,       |
|         |     |                       |                                       | granulomatous disease, inflammatory  |
|         |     |                       |                                       | bowel disease, sepsis, neutropenia,  |
|         |     |                       |                                       | neutrophilia, hemophilia,            |
|         |     |                       |                                       | hypercoagulation, diabetes mellitus, |
|         |     |                       |                                       | endocarditis, meningitis, Lyme       |
|         |     |                       |                                       | Disease, asthma and allergy.         |
| HCWKC15 | 447 | Activation of         | Assays for the activation of          | Highly preferred indications include |
|         |     | transcription through | transcription through the Gamma       | neoplastic diseases (e.g., leukemia, |
|         |     | GAS response element  | Interferon Activation Site (GAS)      | lymphoma, and/or as described        |
|         |     | in immune cells (such | response element are well-known in    | below under "Hyperproliferative      |
|         |     | as T-cells).          | the art and may be used or routinely  | Disorders"). Highly preferred        |
|         |     |                       | modified to assess the ability of     | indications include neoplasms and    |
|         |     |                       | polypeptides of the invention         | cancers, such as, for example,       |
|         |     |                       | (including antibodies and agonists or | leukemia, lymphoma (e.g., T cell     |
|         |     |                       | antagonists of the invention) to      | lymphoma, Burkitt's lymphoma,        |
|         |     |                       | regulate STAT transcription factors   | non-Hodgkins lymphoma, Hodgkin"s     |

| and modulate gene expression          | disease), melanoma, and prostate.       |
|---------------------------------------|-----------------------------------------|
| involved in a wide variety of cell    | breast, lung, colon, pancreatic,        |
| functions. Exemplary assays for       | esophageal, stomach, brain, liver and   |
| transcription through the GAS         | urinary cancer. Other preferred         |
| response element that may be used or  | indications include benign              |
| routinely modified to test GAS-       | dysproliferative disorders and pre-     |
| response element activity of          | neoplastic conditions, such as, for     |
| polypeptides of the invention         | example, hyperplasia, metaplasia,       |
| (including antibodies and agonists or | and/or dysplasia. Preferred             |
| antagonists of the invention) include | indications include autoimmune          |
| assays disclosed in Berger et al.,    | diseases (e.g., rheumatoid arthritis,   |
| Gene 66:1-10 (1998); Cullen and       | systemic lupus erythematosis,           |
| Malm, Methods in Enzymol              | multiple sclerosis and/or as described  |
| 216:362-368 (1992); Henthorn et al.,  | below), immunodeficiencies (e.g., as    |
| Proc Natl Acad Sci USA 85:6342-       | described below), boosting a T cell-    |
| 6346 (1988); Matikainen et al.,       | mediated immune response, and           |
| Blood 93(6):1980-1991 (1999); and     | suppressing a T cell-mediated           |
| Henttinen et al., J Immunol           | immune response. Additional             |
| 155(10):4582-4587 (1995), the         | preferred indications include           |
| contents of each of which are herein  | inflammation and inflammatory           |
| incorporated by reference in its      | disorders. Highly preferred             |
| entirety. Exemplary human T cells,    | indications include blood disorders     |
| such as the SUPT cell line, that may  | (e.g., as described below under         |
| be used according to these assays are | "Immune Activity", "Blood-Related       |
| publicly available (e.g., through the | Disorders", and/or "Cardiovascular      |
| ATCCTM).                              | Disorders"), and infection (e.g., viral |
|                                       | infections, tuberculosis, infections    |
|                                       | associated with chronic                 |
|                                       | granulomatosus disease and              |
|                                       | malignant osteoporosis, and/or an       |
|                                       | infectious disease as described below   |
|                                       | under "Infectious Disease"). An         |
|                                       | additional preferred indication is      |
|                                       | idiopathic pulmonary fibrosis.          |
|                                       | Preferred indications include anemia,   |
|                                       | pancytopenia, leukopenia,               |
|                                       | thrombocytopenia, acute                 |

| phymboruje memini (ALL), plasmacyomas, multiple myeloma- nethrins, ADIS, gramilomenous adisease, inflarmanory-bowed disease, sepsis, neuropenia, neuropenia, neuropenia, powirasis, appassission of immune reactions to transplanted organs and instanse, homophilita, hyperoouglaiston, diabetes mellitus, condocatalis, armongials, tyme Disease, and astimu and allerge, and astimu and allerge. | Assays for the activation of matterport characteristic and another activation through the Ninchest Pool of disorders (e.g., as Factor A, Advitented TOS (NAY).  Best Factor A, Advitented TOS (NAY).  The art and may be used or routnicely the art and may be used or routnicely protective. "Blood-leaf infinity increases dement are well-known in Activity", "Blood-leaf infinity preferred probypopties of the invention) to posteries. It highly preferred probypopties of the invention of indications include attribute and modeline the art and modeline expression of genes involved in immunonedulatory minich expression of genes involved in immunonedulatory minich expression of genes involved in immunonedulatory minich expression of genes involved in immunonedulatory motified to text NFAT expression of genes involved in immunonedulatory motified to text NFAT expression of genes involved in immunonedulatory motified to text NFAT expression of genes proposed expression of genes involved in immunonedulatory motified to text NFAT expression of genes involved in immunonedulatory motified to text NFAT expression of genes in the proposition of the propositi |
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|                                                                                                                                                                                                                                                                                                                                                                                                     | Activation of Assays for Eurascription though transcription though the Cells (such as T-cells). The Cells (such as T-cells) the act an ordified in the Cells (such as T-cells). The Cells (such as T-cells) the Cells (such as T-cells). The Cells (such as T-cells) the Cells (such as T-cells). The Cells (such as T-cells) the Cells (such as T-cells). The Cells (such as T-cells) the Cells (such as  |
|                                                                                                                                                                                                                                                                                                                                                                                                     | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                     | HCWKCIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| include neoplisans and emeers, such the size restangle, ledkermia, yumbioma, and prostate, breast, lung, mooth, procreated, seophageal, and only moreated, seophageal, and only more and preferred indectations include benign dysponilierative deaders and preferred indectations include benign dysponilierative conditions, such as, for example, preparlians, mentalisation and dysplasta. Perferred indications in the processing and the processing of | encurophilia, psoriasis, suppression of immune readions to transplanted organ and tissues, hemophilia, provengalinot, diebets mellins, endocarditis, meningiis, Lyme Dessens, anthra nat allengy.  Highly preferred indications in the blood disorders of successive and the preferred indications in the blood disorders (e.g. as described blood disorders; Handry Standor Cardiovascular Disorders'). Highly perferred indications include blood disorders (e.g. as described blood disorders'). Highly perferred indications include autoimmune diseases (e.g., and or "Cardiovascular Disorders'). Highly perferred indications include autoimmune diseases (e.g., the meanword artificis, systemic lipus erythematods, multiple selensis. |
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| Biophys Acta 1498(1):1-18 (2000);<br>Beb et et al., un 1 Biochem Cell<br>Biol 31(10):1221-1256 (1999);<br>Bester et al., Eurl Jamanol<br>29/38:88-844 (1999); and Yescen et<br>al. Biol Chem (2004); the contents of each of<br>which are better incorporated by<br>reference in its entirety. Teels but<br>which are better forced by<br>reference in its entirety. Teels but<br>which are bester description to these<br>assays are publicly available (e.g.,<br>human Teels that may be used<br>exording to these assays include the<br>SUFT cell line, which is a suspension<br>culture of IL-2 and IL-4 responsive T                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Assays for the activation of Bransaripon through the WIKB response clement are well-known in far and map, be used or routinely modified to assess the ability of forduling amfords and agoniss or anagonists of the invention of reducting amfords and agonis or anagonists of the invention in graphine NRS instruction facus and modified expression of an modified expression of an incumomodulatory genes. Exemplary seasys for transcription                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of Activation of Macarylinou though NFRI response of clement in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 447                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HCWKC15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is         | infection (e.g., AIDS, and/or an<br>infectious disease as described below<br>under "Infectious Disease").<br>Highly preferred indications include         | neoplastic diseases (e.g., melanoma,<br>leukemia, lymphoma, and/or as<br>described below under<br>"Hyperpoliferative Disorders").                               | ringing preciou mercanous menor<br>neoplasms and cancers, such<br>as,melanoma, renal cell carcinoma,<br>leukernia, lymphoma, and prostate,<br>breast, lung, colon, pancreatic,           | esophageal, stomach, brain, liver and<br>urinary cancer. Other preferred<br>indications include benign<br>dysproliferative disorders and pre-  | neoplastic conditions, such as, or<br>example, hyperplasia, metaplasia,<br>and/or dysplasia. Preferred<br>indications also include anemia,<br>pancyoperain, letkoperinia,<br>throm/neov/nnenia. Hodskin's | disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Barditt slymphoma, ardhritis, AlDS, granulomatous disease, inflammatory bowel disease, | sepsis, neutrophilia, psortasis, hemophilia, hyperoagulation, diabetes mellitus, endocarditis, meningitis, Lyme endocarditis, meningitis, Lyme Disease, suppression of immune |
|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| through the NFKB response element that may be used or rountinely modified to test NFKB-response element activity of polypeptides of | the invention (including antibodies<br>and agonists or antagonists of the<br>invention) include assays disclosed in<br>Berger et al. Gene 66:1-10 (1998). | Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6942-6346 (1988); Black et USA 85:6942-6346 (1988); Black et | a., 71ta office 1 (2) 111. (1973). 84. (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that | may be used according to these assays are publicly available (e.g., through the ATCC <sup>TM</sup> ). Exemplary human T cells that may be used | according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.                                                                                  |                                                                                                                                                                  |                                                                                                                                                                               |
|                                                                                                                                     |                                                                                                                                                           |                                                                                                                                                                 |                                                                                                                                                                                          |                                                                                                                                                |                                                                                                                                                                                                           |                                                                                                                                                                  |                                                                                                                                                                               |
|                                                                                                                                     |                                                                                                                                                           |                                                                                                                                                                 |                                                                                                                                                                                          |                                                                                                                                                |                                                                                                                                                                                                           |                                                                                                                                                                  |                                                                                                                                                                               |
|                                                                                                                                     |                                                                                                                                                           |                                                                                                                                                                 |                                                                                                                                                                                          |                                                                                                                                                |                                                                                                                                                                                                           |                                                                                                                                                                  |                                                                                                                                                                               |

| reactions to transplanted organs, asthma and allergy. | A highly preferred embodiment    | of the invention includes a method | for stimulating adipocyte             | proliferation. An alternative highly  | preferred embodiment of the          | invention includes a method for      | inhibiting adipocyte proliferation. | A highly preferred embodiment of    | the invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention           | includes a method for inhibiting     | adipocyte differentiation. A      | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel      | blockage, heart disease, stroke,  |
|-------------------------------------------------------|----------------------------------|------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|---------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|---------------------------------------------|-----------------------------------|
|                                                       | Kinase assay. Kinase assays, for | example an Elk-1 kinase assay, for | ERK signal transduction that regulate | cell proliferation or differentiation | are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the  | invention (including antibodies and | agonists or antagonists of the      | invention) to promote or inhibit cell  | proliferation, activation, and  | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ). Exemplary | mouse adipocyte cells that may be |
|                                                       | Activation of                    | Adipocyte ERK                      | Signaling Pathway                     |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                             |                                   |
|                                                       | 448                              |                                    |                                       |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                             |                                   |
|                                                       | HCWUM50                          |                                    |                                       |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                             |                                   |
|                                                       |                                  | 44                                 |                                       |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                             |                                   |

| inched 713-Li cells 713-Li sen inched 713-Li cells 713-Li sen adherent mouse predipocyte cell line that is continuous substanti of 313 filtrobiast cells developed through todain slashton and undergo a pre-dipocyte to adipose-like a row-weston under appropriate differentiation conditions known in the art. | ys impotence and/or as described below L1 is an under "Immune Activity", Cardiovascular Dislochers", and/or |                                                              | ike disorders (e.g., as described below nder "Neural Activity and | nown in Neurological Discases"), and infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is<br>diabetes mellitus. An additional | highly preferred indication is a | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | (e a due to dishetic neuronathy) | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | hyperglycemic-hyperosmolar coma. | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other discases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine<br>disorders (as described in the |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------|----------------------------------------------------------------------|----------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|-------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                   | used according to these assimplied of 313-L1 cells. 313-adherent mouse preadipoor                           | 3T3 fibroblast cells develor<br>through clonal isolation and | a pre-adipocyte to adipose-l<br>conversion under appropria        | differentiation conditions k                                             | m ar                         |                                                                      |                                  |                                       |                                      |                                   |                                        |                                    |                                      |                                  |                                       |                                 |                                     |                             |                                  |                                     |                           |                                      |                                |                               |                                    |                                                                   |
|                                                                                                                                                                                                                                                                                                                   |                                                                                                             |                                                              |                                                                   |                                                                          |                              |                                                                      |                                  |                                       |                                      |                                   |                                        |                                    |                                      |                                  |                                       |                                 |                                     |                             |                                  |                                     |                           |                                      |                                |                               |                                    |                                                                   |

|  | "Enc    | "Endocrine Disordere" section             |
|--|---------|-------------------------------------------|
|  | 11-11   | torine Figures sector                     |
|  | DEIO    | below), neuropamy, vision                 |
|  | Pas     | and blindness) ulcars and immaired        |
|  | ann     | and binding infection (e.g.               |
|  | infer   | would intention diseases and disorders as |
|  | desc    | described in the "Infectious              |
|  | Dise    | Diseases" section below (particularly     |
|  | ofth    | of the urinary tract and skin). An        |
|  | addi    | additional highly preferred indication    |
|  | dosi    | is obesity and/or complications           |
|  | asso    | associated with obesity. Additional       |
|  | high    | highly preferred indications include      |
|  | weig    | weight loss or alternatively, weight      |
|  | gain.   | . Additional highly                       |
|  | prefi   | preferred indications are                 |
|  | com     | complications associated with insulin     |
|  | resis   | resistance. Additional highly             |
|  | prefi   | preferred indications are disorders of    |
|  | the r   | the musculoskeletal systems               |
|  | inch    | including myopathies, muscular            |
|  | dysti   | dystrophy, and/or as described            |
|  | herein. | in. Additional highly                     |
|  | prefi   | preferred indications include,            |
|  | hype    | hypertension, coronary artery             |
|  | dise    | disease, dyslipidemia, gallstones,        |
|  | osteo   | osteoarthritis, degenerative arthritis,   |
|  | eatin   | eating disorders, fibrosis, cachexia,     |
|  | and     | and kidney diseases or disorders.         |
|  | Prefi   | Preferred indications include             |
|  | neop    | neoplasms and cancer, such as,            |
|  | lymi    | lymphoma, leukemia and breast,            |
|  | color   | colon, and kidney cancer. Additional      |
|  | prefe   | preferred indications include             |
|  | mela    | melanoma, prostate, lung,                 |
|  | panc    | pancreatic, esophageal, stomach,          |
|  | brair   | brain, liver, and urinary cancer.         |

|    |         |     |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Highly preferred indications include liponas and liposacromas. Other preferred indications include benign dysproliferative disorders and preneoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplissia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----|---------|-----|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 45 | HDABR72 | 449 | Adjongte ERK<br>Signaling Pathway | comple an Elle Linnes assay, for chinase assay, for the files with the standard of the coll policitation of differentiation are well known in the art and may be a controlled and or routhfeely and officed to assess the ability of polypeptides of the invention throughting anthodies and agonisis or antagonisis of the articulo 10 ponouse or imbit cell proliferention, activation, and the says of the articular and the says of the articular and a controlled to the says of the articular and a controlled to the says of the articular and a controlled to the says of the articular and agoniss or the invention including anthodies and agoniss or the invention including anthodies and agoniss or an articular and says of the invention include an assays disclosed in forter et al., Biol Chem 379(8-3);1101-1110 Chin and Kanin Almare 410(6824);37-40 (2001); and Cobb Marchan Soc Symp 6429-48 (1999); Marchan Long and Kanin Amure 410(6824);37-40 (2001); and Cobb and the contents of each of vibrid, are been in order to the contents of each of vibrid, are been. | A highly preferred embodiment of the invention includes a method for semanting approaches profileration. An alternative highly preferred embodiment of the invention includes a method for inhibiting adhocyte proliferation. An alternative profileration. An alternative profileration of the invention includes a method for inhibiting adhocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adjocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting includes a method for inhibiting an invention includes a method for inhibiting and invention includes a method for inhibiting the activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating decreasing and/or inactivating decreasing and/or inactivating decreasing and/or inactivating includes regulations, allowed recognistic diseases (e.g., ilponeronia, and/or as ilpones, ilpon |

|                                                                                                                                                       |                                                                                                                                      | "Blood-Related Disorders"), immune<br>disorders (e.g., as described below<br>under "Immune Activity"), neural<br>disorders (e.g., as described below<br>under "Neural Activity and<br>Neurological Diseases"), and                              | incition (e.g., act described below under "Infectious Disease"). An additional signature of the high perfected indication is a dishers enablines. An additional highly preferred indication is a complication associated with dishects explorability, kidney disease (e.g., renal failure, nephropathy. States of disease in dishects explorability, kidney disease (e.g., renal failure, nephropathy and or other diseases and diseases and diseases and disease and nerve disease and barve damage (e.g., due to dishebit neuropathy) nerve disease and nerve disease and barve disease disease disease (e.g., due to dishebit neuropathy) exhaust monthly or blood vessel bloods as well as a condision divension are condisioned and c | microvascular disease hypertension |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC <sup>130</sup> ). Exemplary | mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell | line that is a continuous substrain of 313 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in differentiation conditions known in | the art.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    |
|                                                                                                                                                       |                                                                                                                                      |                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    |
|                                                                                                                                                       |                                                                                                                                      |                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | _                                  |

| _ |  | stroke and other diseases and           |
|---|--|-----------------------------------------|
|   |  | disorders to described in the           |
|   |  | disolucis as described in the           |
|   |  | "Cardiovascular Disorders" section      |
|   |  | below), dyslipidemia, endocrine         |
|   |  | disorders (as described in the          |
|   |  | "Endocrine Disorders" section           |
|   |  | below), neuropathy, vision              |
|   |  | impairment (e.g., diabetic retinopathy  |
|   |  | and blindness), ulcers and impaired     |
|   |  | wound healing, infection (e.g.,         |
|   |  | infectious diseases and disorders as    |
|   |  | described in the "Infectious            |
|   |  | Diseases" section below (particularly   |
|   |  | of the urinary tract and skin). An      |
|   |  | additional highly preferred indication  |
|   |  | is obesity and/or complications         |
|   |  | associated with obesity. Additional     |
|   |  | highly preferred indications include    |
|   |  | weight loss or alternatively, weight    |
|   |  | gain. Additional highly                 |
|   |  | preferred indications are               |
|   |  | complications associated with insulin   |
|   |  | resistance. Additional highly           |
|   |  | preferred indications are disorders of  |
|   |  | the musculoskeletal systems             |
|   |  | including myopathies, muscular          |
|   |  | Š                                       |
|   |  | herein. Additional highly               |
|   |  | preferred indications include,          |
|   |  | hypertension, coronary artery           |
|   |  | disease, dyslipidemia, gallstones,      |
|   |  | osteoarthritis, degenerative arthritis, |
|   |  | eating disorders, fibrosis, cachexia,   |
|   |  | and kidney diseases or disorders.       |
|   |  | Preferred indications include           |
|   |  | neoplasms and cancer, such as,          |
|   |  | lymphoma, leukemia and breast,          |

|    |        |     |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | on, and kidney enter. Additional preferred indications include practicated indications include panceratic, esophageal, stomed, panceratic, esophageal, stomed, them, liver, and trimary cancer, liponase and liposateomas. Other liponase and liposateomas. Other preferred indications include hyporiciterative disorders and opsprolificative disorders and opsprolificative disorders and not no plastic conditions, such as, for no plastic conditions, such as, for any any or dysplastic, and plastic and any or any or dysplastic.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----|--------|-----|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 94 | ШРВАЗВ | 450 | secretion from pancratic beta cells. | insulin are well-known in the art and meaning accuration of answare for measuring accuration of answare based or translution by modified to assess the ability of polypeptides of the process the ability of polypeptides of an agentia or antagonias of the invention (including antibodes in revention. For example, meaning and agentiate meaning and an antibode and agentiate or antagonias of the including anti-ordinal mathodisc less in supendand by galoose and also by certain proteins/peptides, and fails to be stort of the accuration of insulin secretion from patternet of the programment of the process of the invention of insulin secretion from patternet cells by polypeptides of the invention of insulin secretion antagonias of the invention included antagonias of the invention of the invention included antagonias of the invention o | A highly preferred indication is diabetes mellims.  A highly preferred indication is a completion highly preferred indication is a completion associated with diabetes (e.g. diabetic retinopalty, idancy disease (e.g., runt faline, rephropathy idancy disease (e.g., runt faline, rephropathy and obter disease of e.g., runt faline, rephropathy and obter disease and diseated as a described in the 'Renal Disouter's according to the 'Renal Disouter's and their disease, manual consease, independent disease, and their disease, and their disease is and entension, disouters's action entending disouters as a described in the disouters action relational arthrotism and relations and control relations's relationship and control and disouters's action relationship and relationship and and a disouter's section relationship and and a disouter's section relationship and relationship and and a disouter's section relationship and and a disouter's section relationship and relationship and a disouter's section relationship and a disouter's section relationship and relationship |

|   |         |     |                                                | 1995), and HEBS (et al., 197(2):237).  (1995), and Miraglia S et al., doubtuil of Biomedicals Severing, and all discounts of formula of Biomedicals Severing, 41:192-204 (1999), the contents of the and of Visidio is been in nonportated by reference in sis entirely.  By reference in sist antirely, and the analysis of t | "Endocrine Is descenthed in the dischaerier is descenthed in the below, neuropathy, vision below), neuropathy, vision below), neuropathy, vision below), neuropathy, vision mannerner (e.g., diebleic rechnopathy and blindness), utices and impatred and blindness), utices and dischaeries and leiteroners infloctions diseases and dischaeries and blistopers in order the properties of the trimany treat and skin), carpal turner syndrome and Dispoyers is contracture). An additional turner syndrome and Dispoyers is contractured. An additional highly preferred manner to the properties and complications associated with indications include weight use.  Additional highly preferred indications include weight is an Additional highly preferred indications in complications associated with institute resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---|---------|-----|------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2 | HDPBA28 | 450 | Production of TL-10 and activation of T-cells. | Assays for production of IL-10 and accommendate in the accommendate in the art and may be used on in the art and may be used or in the art and may be used or the ability of polypeptides of the ability of polypeptides of the agontists or amagonists of the agontists or amagonists of the production of IL-10 and/or activation production of IL-10 and/or activation may be used or routinely modified to may be used or routinely modified to another and antibodies of the invention (including another accommendate or the invention) to including another accommendation of the invention (including another accommendation).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Highly preferred indications include they are strained and agent and strained with the area of the are |

| iramane response.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly preferred embodiment of the invention includes a method for stimulating adipocyte including a dipocyte discrete and a deferrative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of A stightly preferred embodiment of a stimulating adipocyte proliferation.                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| production and/or T-cell proliferation immune responses disclosed and/or feel in Robinson, leaves said as disclosed and/or cell in: Robinson, fee, and, "The Soylenses an illegac, fee, and," The Soylenses and league, feel and the feel of the feel in the said or the feel of the said." Permanology & Therapenine, St. 154, 156, (2000); He confers type 2 cell-directed therapy feel central morphanel by reference in here in normanic st. 187, 156, (2000); He confers to See a seasy include The Cells tank per least an expending to these assays include The Cells are a feels of the feel are a cleas of T cells that secreted the TLL cells are a fees of the central feel and Let a feels feel are a cleas of T cells that secrete Li. III to III.13.  T cells that secrete that induce differentiation and activation of the letter of the polarizing conditions and suffirm. Primary T helper 2 or and suffirm. | Kinnee seasy, Kinnee seasys, for ceample an Elk-1 kinnee seasy, for ERK signal transluction than tregature of publication or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypopties of the invention (including anthodoses and invention) to polypopties of the invention (including anthodoses and grounsset or attackers). |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Activation of<br>Adipocyte ERK<br>Signaling Pathway                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 451                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HDPB132                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 47                                                                                                                                                                                                                                                                                                                                                                                         |

| An alternative highly preferred embodiment of the invention incidees a method for inhibiting adipoye differentiation. A highly preferred embodiment of the invention includes a method for einvention for the estimulation of       | highly preferred embediment of the intuitive mixed in microtion includes a method for inhibiting the activation of (e.g., decreasing) and or inscribing a method for inhibiting the activation of (e.g., decreasing) and or inscrivating adhosystes. Highly preferred leadurent sequence indications include endocrine liability preferred indications also include neoplastic diseases (e.g., pillapp preferred indications also include neoplastic diseases (e.g., include neoplastic diseases (e.g., include neoplastic diseases (e.g., inspreparationary Diseases). Perferred indications include blood diseases (e.g., inspretrension, e.g., instrumence Activity, neural mixer Timmus Activity, neural endors a described below under "Immune Activity", neural endocreage, heart disease, stroke, inmune e.g., immune Activity, neural endors "Immune Activity", neural endors | Neurological Diseases", and infection (e.g., as described below under "Infections Disease").  A highly preferred indication is |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polyopidies of the invention or polyopidies of the invention | anagonals of the invention) included the assays disclosed in Forner et al. (1998), Le Marchand-Braned Y. Exp (1998), Le Marchand-Braned Y. Exp (1997) in Professional International Professional International Professional International Professional Professional International Professional International Professional International Professional International In | conversion make appropriate differentiation conditions known in the art.                                                       |
|                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                |
|                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                |

| diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease | (e.g., renal fallume, repulvopaths and/or other diseases and disorders and and/or other diseases and disorders' section below), diabetic neuropathy, section below), diabetic neuropathy, rever diseases and nerve damage (e.g., dae to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to | blockage) schrace, mental blockage) schrace, mental blockage) schraces, mental condition, drownlessen, more denoted by pregiverune-hyperosomale comparative schrace (e.g., heart diseases, alteroselerosis, and control schraces, hypertession, struke, and other diseases, hypertession, struke, and other diseases, hypertession, struke, and other diseases and the diseases and the schrace diseases and | catumosacium, tossineris sectuoni<br>belowy, Qsiipdetmia, endocrine<br>generices (sei escribed in the<br>"Endocrine Disorders" section<br>helowy, neuropathy, vision<br>impairment (e.g., diabetic retinopathy<br>and bindrass, ludes and impaired<br>wound healing, infection (e.g.,<br>wound healing, infection (e.g.,<br>wound healing, infection (e.g.,<br>to the uninary treat and slain). An<br>additional highly preferred indication<br>of the uninary treat and slain. An<br>additional highly preferred indication<br>is sessoisated with obesity. Additional<br>is sessoisated with obesity, Additional<br>is sessoisated with obesity, Additional<br>is sessoisated with obesity. Additional |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|   |         |     |                                                                       |                                                                                                                                                                                  | highly preferred indications include gain, Additional highly weight loss or alternatively, weight gain, Additional highly weight effected indications are the complications associated with insulin resistance. Additional highly preferred indications are disorders of including myopathies, muscular depends yasems including myopathies, muscular depends yasems including myopathies, muscular depends with a sea described herein. Additional highly, propertican discharge are described between convergence of include, hypertension, conouncy artery by preferred included in a fall some as described of the control |
|---|---------|-----|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |         |     |                                                                       |                                                                                                                                                                                  | whetcher, exploraged, sounach, brain, iver, and turinay cancer. Highly preferred indications include liponas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplisia, metaphisia, metaphi |
| ≗ | HDPCJ91 | 452 | Activation of Skeletal<br>Mucle Cell P13 Kinase<br>Signalling Pathway | Kinase assay, Kinase assays, for example an GSK-3 kinase assay, for P13 kinase signal transduction that regulate glucose metabolism and cell survivial are well-known in the art | and/or dysplasin.  A highly preferred embodiment of the invention includes a method for increasing muscle cell survival An alternative highly preferred embodimen of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| includes a method for decreasing muscle cell survival. A preferred embodimen of the invention includes a method for crimilaring     |                                                                                                                                                                                                                    | E                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | to Highly preferred inducations included is disorders or the museuboscletal is great. Preferred indications and essentible following the security of the museuboscletal and essentible thou under essentible thou and essentible thou under disorders'), remaid issenses (e.g., as described below under Trabocrine Disorders'), remaid issenses (e.g., as described below under Trabocrine Disorders'), remaid issenses (e.g., as described below under Trabocrine Disorders'), remaid issenses (e.g., as described below under Trabocrine Disorders'), remotological Disorses', blood disorders (e.g., as |
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| and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibudies and aconsists or | chroning antroonic and agonass or an arganists of the invention) to promote or inhibit glucose metabolism and cell survival.  Exemplay assays for P13 kinasi or divitive that most be most becaused or continuous. | modified to test P13 kinase-induced auditive of to test P13 kinase-induced auditive of polypedides of the auditive of polypedides of the invention (including antibodies and agonists or attactions siss of the polypedies of the invention) include assays disclosed in Force et al. Biol Chem 379/88-101. If 01.110.110.01088-Visionijina et proprint programme pr | a. (1. Discuss 49/276-271 (2000), and Schreyer et al. Discuss set 48(2) 166.2 (1999), the contents of each of visible are (1999), the contents in incorporated by reference in its entirety. Mart upoblish ce assistant by to treat according to these assays to the discussing to these assays the publish of according to these assays are the contents of t | ocils that may be used according to<br>these assays include 16 cells. It folia<br>an adhevent transpoliate cells into,<br>isolated from primary cultures of rea<br>traffin musel, or that first to form<br>multimicelened my tubes and strined<br>fibers after culture in differentiation<br>media.                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                     |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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                              |

|  |  | described below under "Immune          |
|--|--|----------------------------------------|
|  |  | Activity", "Cardiovascular             |
|  |  | Disorders", and/or "Blood-Related      |
|  |  | Disorders"), immune disorders (e.g.,   |
|  |  | as described below under "Immune       |
|  |  | Activity"), and infection (e.g., as    |
|  |  | 2                                      |
|  |  | Disease"). A highly preferred          |
|  |  | indication is diabetes mellitus.       |
|  |  | An additional highly preferred         |
|  |  | indication is a complication           |
|  |  | associated with diabetes (e.g.,        |
|  |  | diabetic retinopathy, diabetic         |
|  |  | nephropathy, kidney disease (e.g.,     |
|  |  | renal failure, nephropathy and/or      |
|  |  | other diseases and disorders as        |
|  |  | described in the "Renal Disorders"     |
|  |  | section below), diabetic neuropathy,   |
|  |  | nerve disease and nerve damage (e.g,   |
|  |  | due to diabetic neuropathy), blood     |
|  |  | vessel blockage, heart disease,        |
|  |  | stroke, impotence (e.g., due to        |
|  |  | diabetic neuropathy or blood vessel    |
|  |  | blockage), seizures, mental            |
|  |  | confusion, drowsiness, nonketotic      |
|  |  | hyperglycemic-hyperosmolar coma,       |
|  |  | cardiovascular disease (e.g., heart    |
|  |  | disease, atherosclerosis,              |
|  |  | microvascular disease, hypertension,   |
|  |  | stroke, and other diseases and         |
|  |  | disorders as described in the          |
|  |  | "Cardiovascular Disorders" section     |
|  |  | below), dyslipidemia, endocrine        |
|  |  | disorders (as described in the         |
|  |  | "Endocrine Disorders" section          |
|  |  | below), neuropathy, vision             |
|  |  | impairment (e.g., diahetic retinonathy |

|  | and blindness), ulcers and impaired<br>wound healing, infections (e.g., |
|--|-------------------------------------------------------------------------|
|  | infectious diseases and disorders as                                    |
|  | described in the "Infectious Diseases" section below especially         |
|  | of the urinary tract and skin), carpal                                  |
|  | ×                                                                       |
|  | contracture). An additional<br>highly preferred indication is obesity   |
|  | and/or complications associated with                                    |
|  | obesity. Additional highly preferred                                    |
|  | indications include weight loss or                                      |
|  | alternatively, weight gain.                                             |
|  | indications are complications                                           |
|  | associated with insulin resistance.                                     |
|  | Additional highly preferred                                             |
|  | indications are disorders of the                                        |
|  | musculoskeletal system including                                        |
|  | myopathies, muscular dystrophy,                                         |
|  | and/or as described herein.                                             |
|  | Additional highly preferred                                             |
|  | indications include: myopathy,                                          |
|  | atrophy, congestive heart failure,                                      |
|  | cachexia, myxomas, fibromas,                                            |
|  | congenital cardiovascular                                               |
|  | abnormalities, heart disease, cardiac                                   |
|  |                                                                         |
|  | vascular disease. Highly                                                |
|  | preferred indications include                                           |
|  | neoplasms and cancer, such as,                                          |
|  | rhabdomyoma, rhabdosarcoma,                                             |
|  | stomach, esophageal, prostate, and                                      |
|  | urinary cancer. Preferred indications                                   |
|  | also include breast, lung, colon,                                       |
|  | pancreatic, brain, and liver cancer.                                    |
|  | Other preferred indications include                                     |

| benign dysproliferative disorders and<br>pre-neoplastic conditions, such as,<br>hyperplasia, metaplasia, and/or<br>dysplasia. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                                                                                                               | transacription through the FAS promote element are well-known in the rat and may be used or noutirely monotere element are well-known in the rat and may be used or noutirely monotere element and properties of the invention in modified to assess the ability of polypeptides of the invention in modified to assess the ability of including authorities and agonists or acquired to the FAS promoter element in transcription of the FAS promoter element the ranscription of FAS, at key enzyme transcription of PAS, at key enzyme regulated by many transcription in increases FAS gene transcription in increases FAS gene transcription is also according to the PAS promoter element mee. This simulation of transcription is also strongly as general propertied to the FAS promoter element activity (in Exemplary seasy) what may be used because a continely modified to test for FAS promoter element activity (in invention) include assays disclosed in invention including antibodies and invention including antibodies and general act at 15 (Pt 1) 2577-65 (1999), (Sokonian B. 260); Peterger, et al., Gene 661-10 (1998); Peterger, et al., Gene 661-1 |
|                                                                                                                               | Regulation of Transcription through the FAS promoter element in hepalocytes element in hepalocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                               | 453                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                               | \$9TDAOH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                               | \$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| immunodeficiencies (e.g., as<br>described below). An additional<br>highly preferred indication is<br>infection (e.g., AIDS, and/or an<br>infection diseases and searched below<br>mineral presentations.                                                   | Highly preferred indications include appliate disease (e.g., including opposits disease; (e.g., including opposits) disease; (e.g., including opposite disease) debut and including opposite disease). Typopropilerative Disarders"). "Hypopropilerative Disarders"). "Hypopropilerative Disarders"), "Hypopropilerative Disarders"), such mosphäsms and cancers, such mosphäsms and cancers, such easternate, lymphorn, and prostate, leakernate, lymphorn, and prostate, caschaged, stormed, berän, liver and easternate, propilerative disarders, berän, liver and easternate disarders and easternate disa | indications include benign indications include benign indications include benign metapolishic accepts and pre- cearmple, topochilerative disorders and pre- cearmple, topochilerative disorders and pre- topochilerative disorders and pre- cearmple, topochilerative disorders and and and a pre- indications also include mermit, a processor, and so include mermit, and thrombocytopenia, Hodglein's inframencyopenia, Hodglein's inframencyopenia, Hodglein's inframencyopenia, Indicopenia, ammittiple and arthritis, AIDS, granulomatous diseases, establish controllaria, postraisis, heurophilia, postraisi |
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| that may be used or rountinely modified to test NRFB-response element activity of polypeptides of the invention (including antibodies and agoniss) or antagonisis or differ invention) include assence disclosed in recution) include assence disclosed in | Pergue et al. Grae 66; 110 (1998). Cultur and Mahrim Abelsois in Firzyman 216;542;368 (1998). Firzyman 216;542;368 (1998). USA 85:642-6546 (1988). Black et (1957); and Praser et al., 29(2);838, et (1997); and Praser et al., 29(2);838, et which are herein incorporated by which are herein incorporated by which are bettern incorporated by which are bettern incorporated by where are all and the second of the  | through the ATCCTA, Exemplar, through the ATCCTA, Exemplar, through the ATCCTA, Exemplar, according to the easy include the SUFT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| asthma and allergy. | A highly preferred indication is | diabetes mellitus. An         | additional highly preferred indication | is a complication associated with    | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy     | and/or other diseases and disorders as | described in the "Renal Disorders"   | section below), diabetic neuropathy, | nerve disease and nerve damage     | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to  | diabetic neuropathy or blood vessel | blockage), seizures, mental   | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension, | stroke, and other diseases and      | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine        | disorders (as described in the        | "Endocrine Disorders" section | below), neuropathy, vision        | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired   | wound healing, and infection (e.g.,  | infectious diseases and disorders as | described in the "Infectious    | Diseases" section below, especially   | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's       |
|---------------------|----------------------------------|-------------------------------|----------------------------------------|--------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-------------------------------------|---------------------------------------|----------------------------------|-------------------------------------|-------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|---------------------------------------|-------------------------------|-----------------------------------|----------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|---------------------------------|---------------------------------------|----------------------------------------|---------------------------------------|
|                     | Assays for the regulation of     | transcription through the FAS | promoter element are well-known in     | the art and may be used or routinely | modified to assess the ability of     | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) to       | activate the FAS promoter element in | a reporter construct and to regulate | transcription of FAS, a key enzyme | for lipogenesis. FAS promoter is    | regulated by many transcription       | factors including SREBP. Insulin | increases FAS gene transcription in | livers of diabetic mice. This | stimulation of transcription is also | somewhat glucose dependent.      | Exemplary assays that may be used   | or routinely modified to test for FAS | promoter element activity (in        | hepatocytes) by polypeptides of the | invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed in | Xiong, S., et al., Proc Natl Acad Sci | U.S.A., 97(8):3948-53 (2000); | Roder, K., et al., Eur J Biochem, | 260(3):743-51 (1999); Oskouian B,      | et al., Biochem J, 317 ( Pt 1):257-65 | (1996); Berger, et al., Gene 66:1-10 | (1988); and, Cullen, B., et al.,     | Methods in Enzymol. 216:362-368 | (1992), the contents of each of which | is herein incorporated by reference in | its entirety. Hepatocytes that may be |
|                     | Regulation of                    | transcription through         | the FAS promoter                       | element in hepatocytes               |                                       |                                      |                                       |                                        |                                      |                                      |                                    |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                       |                                      |                                      |                                 |                                       |                                        |                                       |
|                     | 455                              |                               |                                        |                                      |                                       |                                      |                                       |                                        |                                      |                                      |                                    |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                       |                                      |                                      |                                 |                                       |                                        |                                       |
|                     | HDPGT01                          |                               |                                        |                                      |                                       |                                      |                                       |                                        |                                      |                                      |                                    |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                       |                                      |                                      |                                 |                                       |                                        |                                       |
|                     |                                  | 51                            |                                        |                                      |                                       |                                      |                                       |                                        |                                      |                                      |                                    |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                       |                                      |                                      |                                 |                                       |                                        |                                       |

|    |         |     |                                                                                   | as 14HIE cells, are quelies as season as 14HIE cells, are quelies of a season as 14HIE cells, are quelies of wainlies (e.g., through the ATCC**) and/or may be routhing by generated.  Exemplary hepatocytes that may be a coording to these assays include nat liver hepatoms cell lines include and liver hepatoms cell lines include and lines he will procured to the coordinate of the lines in the lines of the li | contracture). An additional subtiliproper distribution and the preferred indication is obesity and or complications associated with indications subtiliproper and indications include weight pass of indications include weight gain. Additional highly preferred Additional highly preferred and indications are complications associated with insulin resistance associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| S. | HDPHISI | 456 | transarition through the FA Spromoter element in hypmosytes element in hypmosytes | transaription through the FAS removaription through the FAS removed element are well-known in the set and may be used or counterly modified to seese it he history modified to seese modified to see the remotion to each who the history modified to history modified to may the modified modified to the story | A highly preferred indication is diachesis mellins, and dischain and additional lightly preferred indication is a complication associated with diaches (e.g., diachetic retinopathy, diachetic repimpathy, fatrory disches in repimpathy, fatrory disches in repimpathy, fatrory disches in repimpathy and disches in the respin part of the respiratory of the respirator of the respiratory of the resp |
|    |         |     |                                                                                   | U.S.A., 97(8):3948-53 (2000);<br>Roder, K., et al., Eur J Biochem,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | "Endocrine Disorders" section<br>below), neuropathy, vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|          |     |                                          | Gene 66:1-10 (1998); Cullen and<br>Malm Methode in Enzamol                 | described below under "Hymenyoliferative Disorders")                        |
|----------|-----|------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
|          |     |                                          | 216:362-368 (1992); Henthorn et al.,                                       | Preferred indications include                                               |
|          |     |                                          | 6346 (1988); Georas et al., Blood                                          | neopiasms and cancers, sucn as,<br>leukemia, lymphoma, melanoma, and        |
|          |     |                                          | 92(12):4529-4538 (1998); Moffatt et                                        | prostate, breast, lung, colon,                                              |
|          |     |                                          | al., Transplantation 69(7):1521-1523                                       | pancreatic, esophageal, stomach,                                            |
|          |     |                                          | (2000); Curiel et al., Eur J Immunol<br>27(8):1982-1987 (1997); and Masuda | pram, inver and urmary cancer. Omer<br>preferred indications include benign |
|          |     |                                          | et al., J Biol Chem 275(38):29331-                                         | dysproliferative disorders and pre-                                         |
|          |     |                                          | 29337 (2000), the contents of each of                                      | neoplastic conditions, such as, for                                         |
|          |     |                                          | which are herein incorporated by                                           | example, hyperplasia, metaplasia,                                           |
|          |     |                                          | may be used according to those                                             | and/or dysplasia.  Professed indications include anomia                     |
|          |     |                                          | assays are publicly available (e o                                         | nanostonenia lenkonenia                                                     |
|          |     |                                          | through the ATCCTM). Exemplary T                                           | thrombocytopenia, Hodekin's                                                 |
|          |     |                                          | cells that may be used according to                                        | disease, acute lymphocytic anemia                                           |
|          |     |                                          | these assays include the SUPT cell                                         | (ALL), plasmacytomas, multiple                                              |
|          |     |                                          | line, which is a suspension culture of                                     | myeloma, Burkitt's lymphoma,                                                |
|          |     |                                          | IL-2 and IL-4 responsive T cells.                                          | arthritis, AIDS, granulomatous                                              |
|          |     |                                          |                                                                            | disease, inflammatory bowel disease,                                        |
|          |     |                                          |                                                                            | sepsis, neutropenia, neutrophilia,                                          |
|          |     |                                          |                                                                            | psoriasis, suppression of immune                                            |
|          |     |                                          |                                                                            | reactions to transplanted organs and                                        |
|          |     |                                          |                                                                            | tissues, hemophilia,                                                        |
|          |     |                                          |                                                                            | hypercoagulation, diabetes mellitus,                                        |
|          |     |                                          |                                                                            | litis, menin                                                                |
|          |     |                                          |                                                                            | Disease. An additional                                                      |
|          |     |                                          |                                                                            | preferred indication is infection (e.g.,                                    |
|          |     |                                          |                                                                            | an infectious disease as described                                          |
| HINDINGO | 157 | Production of MCP 1                      | MCD I BMAT Assesse for                                                     | A highly mefered embodiment of                                              |
| 0.000    | 1   | 1 10 10 10 10 10 10 10 10 10 10 10 10 10 | imminomodulatory proteins that are                                         | the invention includes a method for                                         |
|          |     |                                          | produced by a large variety of cells                                       | stimulating (e.g., increasing) MCP-1                                        |
|          |     |                                          | and act to induce chemotaxis and                                           | production. An alternative highly                                           |
|          |     |                                          | activation of monocytes and T cells                                        | preferred embodiment of the                                                 |

|                                      |                                    |                                     | 8                                     |                              |                             | p                                    | p                                 |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   | Ţ                                      | ,î                                   |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 | oʻ                                   |                                    |                                    | _                                    |                                  |                                      |                                     |                                   |                                   | _                                     |
|--------------------------------------|------------------------------------|-------------------------------------|---------------------------------------|------------------------------|-----------------------------|--------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|------------------------------------|-------------------------------|------------------------------------|---------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|-------------------------------|-----------------------------------|-------------------------------------|------------------------------|---------------------------------|--------------------------------------|------------------------------------|------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|---------------------------------------|
| invention includes a method for      | production. A highly preferred     | indication is infection (e.g., an   | infectious disease as described below | under "Infectious Disease"). | Additional highly preferred | indications include inflammation and | inflammatory disorders. Preferred | indications include blood disorders | (e.g., as described below under     | "Immune Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"). Highly preferred | indications include autoimmune     | diseases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,     | multiple sclerosis and/or as described | below) and immunodeficiencies (e.g., | as described below). Preferred        | indications also include anemia,      | pancytopenia, leukopenia,              | thrombocytopenia, Hodgkin's   | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple      | myeloma, Burkitt's lymphoma, | arthritis, AIDS, granulomatous  | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, | psoriasis, suppression of immune   | reactions to transplanted organs and | tissues, hemophilia,             | hypercoagulation, diabetes mellitus, | endocarditis, meningitis (bacterial | and viral), Lyme Disease, asthma, | and allergy Preferred indications | ales include negationic diceoces (a c |
| are well known in the art and may be | the ability of polypeptides of the | invention (including antibodies and | agonists or antagonists of the        | invention) to mediate        | immunomodulation, induce    | chemotaxis, and modulate immune      | cell activation. Exemplary assays | that test for immunomodulatory      | proteins evaluate the production of | cell surface markers, such as     | monocyte chemoattractant protein   | (MCP), and the activation of  | monocytes and T cells. Such assays | that may be used or routinely         | modified to test immunomodulatory | and differentiation activity of        | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Miraglia et al., J | Biomolecular Screening 4:193- | 204(1999); Rowland et al.,        | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000);    | Satthaporn and Eremin, J R Coll | Surg Ednb 45(1):9-19 (2001); and     | Verhasselt et al., J Immunol       | 158:2919-2925 (1997), the contents | of each of which are herein          | incorporated by reference in its | entirety. Human dendritic cells that | may be used according to these      | assays may be isolated using      | techniques disclosed herein or    | othorwice brown in the ort Human      |
|                                      |                                    | _                                   |                                       |                              |                             | _                                    |                                   |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   |                                        |                                      |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 |                                      |                                    |                                    |                                      |                                  |                                      |                                     |                                   |                                   |                                       |
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|                                      |                                    |                                     |                                       |                              |                             |                                      |                                   |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   |                                        |                                      |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 |                                      |                                    |                                    |                                      |                                  |                                      |                                     |                                   |                                   | -                                     |

| tenkemia, lymphoma, and/or as seekrebe dolew under er-sterbed below under er-sterbed below under er-sterbed below under high preferred indications include neoplesars and eancers, such as, the seekrebens, lung, colon, prontendic, bereas, lung, colon, promeratio, escaplagen, issumen, henin, liver, and unimary cancer. Other proferred indications include benign indications include benign indications include benign includes benign include benign incomplisatio conditions, such as, for neoplesite conditions, such as, for morphishis, and or dysplasia. | A highly preferred indication is dishetes mellius.  A highly preferred indication is a compilation highly perferred indication is a compilation associated with dishetest (e.g., dishetest et galledist retinopally, dishetest et galledist retinopally, dishetest et galledist retinopally, dishetest engalement et galledist et and indicate and there is men in the "Rema Disonders" secure below), dishetest menopally, nerve diseases and durete damage (e.g., due to dishete to amopally, nerve disease and nerve damage of extra disease, can the ordineder teamopally, blood vessel blockegs, heart diseases, cannot contision, drowsiness, montal contision, drowsiness, mental c |
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| dendriic cells are antigen presenting cells in suspension culture, which, when such such and or collection and or collections; minine and upregulate T cell politication and functional activities.                                                                                                                                                                                                                                                                                                                                                                   | transcription through the FAS rounder element are well-known in the art and may be used or rountingly the art and may be used or rountingly the art and may be used or rountingly polyperpides of the invention polyperpides of the invention polyperpides of the invention (including ampleodies and agoniss or antagoniss of the invention in serious the FAS promoter element in serious the FAS promoter element in serious the FAS promoter element in transcription of PAS, a key enzyme transcription in increase FAS gone transcription in increase FAS gone transcription is also securing the serious in also securing the serious properties of the serious including of the transcription is also securing a dispersion of transcription in selec- strain transcription in selec- strain transcription in selec- tion of transcription in selection of transcription in selec- transcription in the selection of transcription in selec- transcription in the selection of transcription in selec- transcription in the selection of selection of transcription in selection of transcri |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | transarrijeon though the FAS promoter clement in hepatocytes clement in hepatocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 457                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HIDPIM50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ଜ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| important in the pathogenesis of | asthma. Exemplary assays for | transcription through the NFKB | response element that may be used or | rountinely modified to test NFKB- | response element activity of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Marone et al, Int Arch | Allergy Immunol 114(3):207-17 | (1997), the contents of each of which | are herein incorporated by reference | in its entirety. Cells were pretreated | with SID supernatants or controls for | 15-18 hours, and then 10 ng/mL of | TNF was added to stimulate the | NFkB reporter. SEAP activity was | measured after 48 hours. Basophils | that may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary | human basophil cell lines that may be | used according to these assays | include Ku812, originally established | from a patient with chronic | myelogenous leukemia. It is an | immature prebasophilic cell line that | can be induced to differentiate into | mature basophils. See, Kishi et al., | Leuk Res. 9:381-390 (1985); Blom et | al., Eur J Immunol, 22:2025-32 |
|----------------------------------|------------------------------|--------------------------------|--------------------------------------|-----------------------------------|------------------------------|-------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|--------------------------|--------------------------------------|---------------------------------|-------------------------------------|-------------------------------|---------------------------------------|--------------------------------------|----------------------------------------|---------------------------------------|-----------------------------------|--------------------------------|----------------------------------|------------------------------------|-------------------------------------|--------------------------------------|--------------------------------|---------------------------------------|--------------------------------|---------------------------------------|-----------------------------|--------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|
|                                  |                              |                                |                                      |                                   |                              |                               |                                       |                                       |                                    |                                 |                          |                                      |                                 |                                     |                               |                                       |                                      |                                        |                                       |                                   |                                |                                  |                                    |                                     |                                      |                                |                                       |                                |                                       |                             |                                |                                       |                                      |                                      |                                     |                                |
| _                                |                              |                                |                                      |                                   |                              |                               |                                       |                                       |                                    |                                 |                          |                                      |                                 |                                     |                               |                                       |                                      |                                        |                                       |                                   |                                |                                  |                                    |                                     |                                      |                                |                                       |                                |                                       |                             |                                |                                       |                                      |                                      |                                     | _                              |
|                                  |                              |                                |                                      |                                   |                              |                               |                                       |                                       |                                    |                                 |                          |                                      |                                 |                                     |                               |                                       |                                      |                                        |                                       |                                   |                                |                                  |                                    |                                     |                                      |                                |                                       |                                |                                       |                             |                                |                                       |                                      |                                      |                                     |                                |

|                                                                                          | he highly perfected embodiment of the inversion includes a method for increasing addrocyte sarrival Am embodiment of the inversion includes a method for increasing addrocyte sarrival Am embodiment of the invention includes a method for decreasing adjocyte sarrival. A preferred and procyte positivation and adjocyte positivation. An adjocyte positivation of the invention includes a method for inhibiting adjocyte differentiation. An adjocyte positivation of the invention includes a method for inhibiting adjocyte of inferentiation. An alternative bighly preferred method for inhibiting preferred indications include in receiptation includes a method for inhibiting preferred indications include and oversible flow under "Endocrine disacresic (e.g., six perferred indications include recopulation diseases (e.g., hyperpentiation, blood disacres (e.g., hyperpentiation in adjocyte congressive heart failure, blood vessel bloodege, heart disease, stroke of bookers.) Perfect of midpocures and or as described below under "Endocrine Biotoges," and the sease, stroke, and or as described below under "Endocrine Biotoges," and the sease, stroke, and or as described below under "Endocrine Biotoges," and sease and or as described below under "Endocrine Biotoges," and failure in propriettion and or as described below under "Endocrine Biotoges," and failure blood vessel biotoges, beart disease, stroke in propriettion and or as described below under "Endocrine Biotoges," and failure and or as described below under "Endocrine Biotoges," and failure and or as described below under "Endocrine Biotoges," and described below und |
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| (1992), where the contents of each are herein incorporated by reference in its entirety. | ceample an GSK-3 assays, for example an GSK-3 assays, for P15 kinnes stignal transduction that regular glucose metabolisms and cell sequilar glucose metabolisms and cell amount of the formation of the invention to promote or inhibit glucose. Exemplary assays for P15 kinase-deal starvisal. Exemplary assays for P15 kinase-deal starvisal. Exemplary assays for P15 kinase-deal starvisal of the invention of the total of the invention of the total of the invention of the days of the assays disclosed in invention (including and easys) (sistemin et al., Diabetes 44/2), 265-27 (2000). The contents of cach of which are better in its entiry. Mouse adipocyte cells that may be used according to these starving on these and excepting to these according to the contents and according to these according to the contents according to these according to the contents according to these according to these according to the contents according to the contents according to the contents according to these according to the contents  |
|                                                                                          | Activation of Activation of Signalling Pathway Signalling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                          | 458                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                          | HDNU46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                          | ¥                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| line that is a continous substrain of | "Cardiovascular Disorders", and/or     |
|---------------------------------------|----------------------------------------|
| 3T3 fibroblast cells developed        | "Blood-Related Disorders"), immune     |
| through clonal isolation and undergo  | disorders (e.g., as described below    |
| a pre-adipocyte to adipose-like       | under "Immune Activity"), neural       |
| conversion under appropriate          | disorders (e.g., as described below    |
| differentiation conditions known in   | under "Neural Activity and             |
| the art.                              | Neurological Diseases"), and           |
|                                       | infection (e.g., as described below    |
|                                       | under "Infectious Disease"). A         |
|                                       | highly preferred indication is         |
|                                       | diabetes mellitus. An                  |
|                                       | additional highly preferred indication |
|                                       | is a complication associated with      |
|                                       | diabetes (e.g., diabetic retinopathy,  |
|                                       | diabetic nephropathy, kidney disease   |
|                                       | (e.g., renal failure, nephropathy      |
|                                       | and/or other diseases and disorders as |
|                                       | described in the "Renal Disorders"     |
|                                       | section below), diabetic neuropathy,   |
|                                       | nerve disease and nerve damage (e.g,   |
|                                       | due to diabetic neuropathy), blood     |
|                                       | vessel blockage, heart disease,        |
|                                       | stroke, impotence (e.g., due to        |
|                                       | diabetic neuropathy or blood vessel    |
|                                       | blockage), seizures, mental            |
|                                       | confusion, drowsiness, nonketotic      |
|                                       | hyperglycemic-hyperosmolar coma,       |
|                                       | cardiovascular disease (e.g., heart    |
|                                       | disease, atherosclerosis,              |
|                                       | microvascular disease, hypertension,   |
|                                       | stroke, and other diseases and         |
|                                       | disorders as described in the          |
|                                       | "Cardiovascular Disorders" section     |
|                                       | below), dyslipidemia, endocrine        |
|                                       | disorders (as described in the         |
|                                       | "Endocrine Disorders" section          |
|                                       | below), neuropathy, vision             |

| impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's | contracture). An additional | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | indications are disorders of the | musculoskeletal systems including | myopathies, muscular dystrophy, | and/or as described herein. | Additional highly preferred | indications include, hypertension, | coronary artery disease, | dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, | eating disorders, fibrosis, cachexia, | and kidney diseases or disorders. | Highly preferred indications include | neoplasms and cancer, such as, | lipoma, liposarcoma, lymphoma, | leukemia and breast, colon, and | kidney cancer. Additional highly | preferred indications include | melanoma, prostate, lung, | nancreatic esonhageal stomach |
|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|-------------------------------------|----------------------------------------|---------------------------------|-----------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|-----------------------------------|---------------------------------|-----------------------------|-----------------------------|------------------------------------|--------------------------|---------------------------|-----------------------------------------|---------------------------------------|-----------------------------------|--------------------------------------|--------------------------------|--------------------------------|---------------------------------|----------------------------------|-------------------------------|---------------------------|-------------------------------|
|                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                    |                          |                           |                                         |                                       |                                   |                                      |                                |                                |                                 |                                  |                               |                           |                               |
|                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                    |                          |                           |                                         |                                       |                                   |                                      |                                |                                |                                 |                                  |                               |                           |                               |
|                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                    |                          |                           |                                         |                                       |                                   |                                      |                                |                                |                                 |                                  |                               |                           | _                             |

|   |         |     |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | brain, liver, and urinary cancer. Other perferred indicators include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---|---------|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * | HDPND46 | 885 | Production of IL-4 | ILL-HWMT Assays for immanoancellatory proteins secreted by TH2 cells that stimulate b cells. The cells immanoancellatory proteins secreted by TH2 cells that stimulate b cells. The cells immanoancellatory proteins secreted and promote polarization of CD44 and promote polarization of CD44 and the standard may be used or in the strained may be used or in the ability of polypeptides or the animation cells and the ability of polypeptides of the immanoancellation stimulation of immano or cell-incidiated immanity or cell-incidiated immanity or cell-incidiated immanity or cells. The and the atimulation of immanoancellatory in animation of immanoancellatory in the animation of animation anima | A highly preferred embodiment for the invention includes a method for stimulating (e.g., increasing) IL—4 production. An informative highly preferred embodiment of the inhibiting (e.g., reducing) IL—4 production. A highly preferred demodration of the inhibiting (e.g., reducing) IL—4 production. A highly preferred indication includes suffame. A highly preferred indication includes suffame. A highly preferred indication includes suffame and indication includes in the inhibition of the inhibition include indications include inflammatory deaded: Eighty preferred indications include inflammatory deaded. Highly preferred indications include inflammatory deaded in the inhibition of the conferred indications include exceptible below that symptoms, mechanism and prostate, these, lung, someth, brain, liver and trining someth, brain, liver and training enables being appropriate in the inhibition of the profetred indications and prevently latest disorders and preve |
|   |         |     |                    | Biomolecular Screening 4:193-204 (1999); Rowland et al.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | conditions, such as, for example,<br>hyperplasia, metaplasia, and/or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|    |         |     |                                                                                                          | Chapter 61, 38-160 (2000); Gonzalez- Chapter 61, 38-160 (2000); Gonzalez- de al. J (Tile Jan Anta (8), 2777-283 (1194); Viewele et al., Res hummon (1194); Viewele et al., Res hummon (1949); Ragley et al., Net hummon (107, 257-261 (2000); Madwal and red formiff et al., Rost hummon (107, 257-261 (2000); Madwal and Perci incorporated by reference in sentiery. Human Tectronec in the machan collected herein or otherwise known in the art. Human Tectronec is human to end by many and express a Tell receptor and the hymans and express a Tell receptor mediate humand to cell-mediated mediate human or cell-mediated in mediate human or cell-mediated in immunormodulatory factors. | include blood disorders (e.g., as decebred indications include blood disorders (e.g., as described bloow under "Immune Activity", "Shood-Relaned Indications include auditorial and a "Cardiovascular Disorders", Preferred indications include auditmune diseases (e.g., include auditmune disease). Preferred inmuned efficiencies (e.g., include auditmuned efficiencies (e.g., include auditmuned efficiencies (e.g., include auditmuned efficiencies (e.g., include auditmuned efficiencies include aucmin, throughous, leaders properties audities audities audities audities audities audities, Audition audities audities, Audities desse Arm adities, audities au |
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| 54 | HDPND46 | 458 | Production of IL-8 by<br>by endothelial cells<br>(such as Human<br>Umbilical Cord<br>Endothelial Cells). | Assays measuring production of IL-8 are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | minches and minches as altergy, assume, elektrain, etc. and as assume, leukernia, etc. and as described below under "Immune Activity", and "Blood-Related Disorders"). Highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| inflications also include autoimmune disooctav (e.g., rheumanoid artiriis, systemic hipus erythemaosia, systemic hipus erythemaosia, systemic hipus erythemaosia, systemic hipus erythemaosia, systemic mulpie selensis and/or as desarrhed below, mulpe selenthe below, emocras sach as ling, liver, colon emocras sach as ling, liver, colon emocras, and or adesarrhed below muler "Hyperprofilerative emocras, and or adesarrhed below muler "Hyperpositions and entitions and single hipus and exception and separation of the state respiratory distress syndrome and consequent experience is shortine expertition as systemic is shortine expertition respiratory distress syndrome and expertition respiratory distress syndrome and experience of the state respiratory distress syndrome and experience is shortine expertition respiratory distress syndrome and experience of the state of the  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| and/or secretion of IL.8. For country, my be used or pountry! modified to assess the him of the properties of the invention (including anthodies of the invention (including anthodies and the invention) to regulate production and or secretion of IL-8 from endothedial cells, each as human endothedial cells (each as human endothedial cells, which line venous blood vessels, and are involved in minicators that inducted, but are not limited to, agiogenesis, vascular limited to, agiogenesis, vascular more minication that produced the internet billy, vascular tone, and immune cell extravastic note, and immune cell extravastic not, in the initiation and perpetuation of inflammation and secretion of inflammation of inf | regulatory and coding sequence of<br>guarders syndraces, the first specific<br>enzygue in the cholesterol<br>solvoyated in the cholesterol<br>enzygue in the cholesterol<br>solvoyated in the cholesterol<br>al., 1 Biol. Chem. 268:1281.8<br>1 12624 (1993), the contents of which<br>we better in from the contents of which<br>in its entirety. Calls were treated<br>in its entirety. Calls were treated<br>in sits entirety. Calls were treated<br>in the cholesterol and the cholesterol<br>activity was measured after 72 hours.<br>HerCit as the man hepatocellular<br>earcinoms eed line (ATCCW HB). |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Inhibition of squalene<br>synthetase gene<br>transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 459                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPOJ08                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | \$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|               |     |                                                   | 8065). See Knowles et al., Science.<br>209:497-9 (1980), the contents of<br>which are herein incorporated by<br>reference in its entirety.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| \$<br>HDPOJ08 | 459 | Regulation of spoptosis in paracretic beta cells. | Compase Apoptosis. Assays for caspase apoptosis as a continuor the art and may be used to continuor the art and may be used to continuor properpitedes of the invention polyperpitedes of the invention) to polyperpitedes of the invention) to polyperpitedes of the invention) to managonists of the invention) to promote caspase proteose-mediated apoptosis. Apoptosis in pamerasitic apoptosis. Apoptosis in pamerasitic progression of title decision and progression of title decision. The progression of title decision are apoptosis, Apoptosis in pamerasitic progression of title for invention) include the assays disclosed in: Loweth, AC. et al., EBSI Lett. 460(1):229-56 (1996); Kantidonia, and the assays disclosed in: Loweth, AC. et al., EBSI Lett. 46(1):229-56 (1996); Kantidonia, and the assays disclosed in: Loweth, AC. et al., BESI Lett. 45(2):229-56 (1996); Kantidonia, Caloni, Salk K. et al., Il Immunol, 16(607)-4481-9 (2001); Tegelsol, et al., 1781 Lett. 459(2):238-43 (1909); Mang. S. et al., 1781 Lett. 459(2):238-43 (1909); Mang. S. et al., 1781 Lett. 459(2):238-43 (1909); Mang. S. et al., 1781 Lett. 459(2):238-43 (1900); Mang. S. et al., 1781 Lett. 459(2):248-24 (1900); Mang. Mang. | A highly preferred indication is adiabeted mellina and diabeted mellina and additional highly preferred indication and additional highly preferred indication and additional negative and an analysis of the analysis of a completional and on the analysis of a completional plants and on the analysis of a completion and on the analysis of a completion and on the analysis of a completion and and on the analysis of a completion and an analysis of a completion and other diseases and disease, and other diseases and disease, hyperphysical properties of a plant of the analysis of a continsion, devested the association of a continsion, devested the association and other diseases and disease, and other diseases and disease, and other diseases and disease, and other diseases and disea |

| - 1 | of the urinary tast and skin), carpal under synchronization and papers and papers in a manner synchronization and papers in a manner synchronization and papers in a manner synchronization associated with and one of the papers include weight nose or differentively, wedging gain.  Additional highly preferred differentively, weight gain.  Additional highly preferred indications are complications as associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | A highly preterned indication is disheters mellitus.  A highly preterned indication is a double mellitus.  The proper mellitus is a complication associated with dishetes (e.g., dishetic retinopathy, there of disease (e.g., read in failure, rephropathy and con the relasses and disheders as described in the 'Renail Disonders' and over disease and herve dismage (e.g., area of merve dismage (e.g., area of blocking; heart disease, blocking; heart disease, when the read of the property or block vessel blocking, heart disease, when improperty or block of vessel blockings, heart disease, and dishetic neuropathy or block of vessel blockings, heart disease, and dishetic neuropathy or block vessel blockings, beartons, mental contilistic. dowsitess, mental contilistic. dowsitess, mental contilistic. dowsitess, mental contilistic.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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|     | 1990; the comments of each of which are berein incorporated by reference with a securities of last entirely, because the securities of the | Assays for measuring secretion of insulin or well-known in the art and may be used or routinely modified on sesses the shifts of polypythics of the invention (including untabodies of the invention (including untabodies or the invention) to stimulate insulin secretion. For example, insulin secretion is nearable, insulin secretion for similar antibodies in sensatured by PMAT insulin secretion from panceaulic beta of each is ingegulated by glucose and also by certain proteins/porticias, and distincts. Exemplary sesses that may distincted the places with the control of the |
|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | secretion from pancrenic bear cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 460                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPPN86                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 95                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|         |     |                                                                    | polypeptides of the invention properties of the invention of the chiefly and polypeptides of the invention) include assays disclosed in. Ahren, B., et al., and proposition of the invention) include assays disclosed in. Ahren, B., et al., Endocranology, H. M., et al., Endocranology, E. M., et al., E. M., et al., E. M., et al., E. M., et al., | endiovascular disease (e.g., heart candiovascular disease) (e.g., heart microwascular disease), hypertension, stroke, and other diseases and deductive as described in the "Cardiovascular Disorders" section disorders" section disorders" section disorders (as described in the "Cardiovascular Disorders" section disorders" section below), despitiental, endocrine disorders, described in the below, described in the below, entropathy, vision below), entropathy, vision below), and plinderses) alters and direction (e.g., microtion sitesaes and donders as described in the "Infection (e.g., microtions diseases and donders as described in the "Infections as described in the "Infections as described in the "Infections of the urmany tact and skin), carpillar thanks syndrome and Dispuytorn's contracture). An additional highly preferred discussion susciented with indications in obesity. Additional highly preferred discussions microtions resulted to sor enternatively, weight gan.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------|-----|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |     |                                                                    | astilinoma. In these cents retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | aucmanvety, weign gain. Aditional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| HDPSB18 | 461 | Stimulation of insulin<br>secretion from<br>pancreatic beta cells. | Endocration[ogy 192; 193; 167. Assays for measuring secretion of insulin are well-known in the art and may be used or nouninely modified to assesse the ability of polypeptides of the invention (including antibodies and agonists or antagonists or the invention) to simulate insulin invention) to simulate insulin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | A highly preferred indication is diabetes melltins. An diabetes melltins. An additional lightly preferred indication is a complication associated with diabetes (e.g., diabetic redinopathy, diabetic melliopathy, isdiney disease (e.g., rend failure, nephropathy and a failure in property and a failure in the failure |

| s as                                   |                                    | ķ,                                   |                                        |                                     | s,                                     |                                     | 귱                                   |                                       |                                      | g,                               |                                     |                                       | эп,                                   |                                         |                                   | п                                      |                                   |                                 |                                  |                                    | ıthy                                   | Ģ                                    | . £                                 | S                                    |                                        | ×                                    | 귾                                      |                                     |                                   | ity                                    | Ħ                                    | pa                                   |                                     |                                |                                   |   |
|----------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|-----------------------------------|---|
| es and disorde                         | enal Disorders                     | betic neuropat                       | erve damage                            | c neuropathy)                       | ige, heart dise:                       | e.g., due to                        | or blood vess                       | , mental                              | ess, nonketotic                      | erosmolar cor.                   | ase (e.g., hear                     | osis,                                 | ase, hypertens:                       | seases and                              | ed in the                         | sorders" section                       | ia, endocrine                     | bed in the                      | ers" section                     | v, vision                          | iabetic retinop                        | ers and impair                       | infection (e.;                      | and disorders                        | fections                               | elow, especial                       | and skin), carj                        | d Dupuytren,                        | An additional                     | dication is obe                        | ns associated v                      | l highly prefer                      | weight loss or                      | nt gain.                       | ејетер                            |   |
| and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | nyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | selow), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious           | Diseases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture).                     | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or  | alternatively, weight gain     | Aditional highly preferred        |   |
| an                                     | g                                  | sec                                  |                                        |                                     | -                                      | _                                   | _                                   | _                                     | Ť                                    | hy                               | _                                   | _                                     | _                                     |                                         | Ť                                 | ÷                                      | ÷                                 | dis                             | _                                | _                                  | _                                      |                                      | WC                                  | _                                    | Ť                                      | _                                    | Ť                                      | _                                   | Ť                                 |                                        | an                                   | _                                    |                                     | alt                            | V                                 |   |
| , insulin                              | y FMAT                             | tibodies.                            | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | þý                               | notion                              | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | ):237-9                         | ct. al.,                         | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | ety.                                | y be used                            | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | line                                 | established from cells isolated from | an X-ray induced rat transplantable | s retain                       | fnative                           |   |
| r example                              | easured by                         | insulin an                           | ion from p                             | alated by g                         | n proteins/                            | is a key co                         | emplary as                          | ntinely mo                            | n of insuli                          | tic cells) l                     | of the inve                         | ibodies ar                            | the inven                             | ed in: Ah                               | , 277(4 Pt                        | ., ct al., Er                          | 40 (1997);                        | ett, 377(2                      | Miraglia S                       | omolecula                          | 999), the c                            | i is herein                          | n its entire                        | lls that ma                          | hese assay                             | ., through                           | e routinely                            | ncreatic o                          | ding to the                       | S-1 cells.                             | herent cell                          | om cells is                          | iced rat tra                        | These cells                    | s typical o                       |   |
| secretion. For example, insulin        | secretion is measured by FMAT      | using anti-rat insulin antibodies.   | ulin secret                            | ls is upregr                        | by certain                             | regulation                          | betes. Exe                          | used or rou                           | stimulatio                           | (from pancreatic cells) by       | polypeptides of the invention       | cluding an                            | agonists of                           | ays disclos                             | J Physiol                         | 99); Li, M                             | (9):3735-                         | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S et. al., | rnal of Bio                        | 93-204 (19                             | h of which                           | by reference in its entirety.       | Pancreatic cells that may be used    | ording to 1                            | ilable (e.g                          | Vor may be                             | emplary pa                          | used accor                        | lude rat IN                            | are a semi-adherent cell line        | ablished fr                          | X-ray indu                          | insulinoma. These cells retain | characteristics typical of native |   |
| sec                                    | sec                                | usi                                  | Insi                                   | cell                                | alsc                                   | disi                                | dia                                 | Ę.                                    | for                                  | Œ)                               | lod                                 | ij                                    | aut                                   | ass                                     | An                                | (1)                                    | 138                               | cta                             | (1)                              | lon                                | 4:1                                    | eac                                  | ρÃ                                  | Pan                                  | acc                                    | ava                                  | and                                    | Exc                                 | Бе.                               | inc                                    | arc                                  | est                                  | an                                  | insi                           | cha                               |   |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |   |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |   |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |   |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |   |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   | - |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |   |
| _                                      |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   | _ |
|                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |   |

| asso                                                                                       | A highly preferred indication is distense mellins additional highly preferred indication and distense mellins a editional highly preferred indication as a compleaning associated with distores (e.g., distort crimopathy, dataset distorts or and failure, trephropathy kinds orders as addy or the failure, trephropathy shared search and failure, trephropathy shared search below, distort and there distorts as addy or the failure, trephropathy is nerve diseases and teave damage.  The state of the sease of the sease and described in the variety of the seases and the sease and the sease of the seases and experients on the sease of the seases of the |
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| glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                            | Simulation of Calcium Flux in pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                            | 462                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                            | HDPSHE3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                            | 88                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| Per used according to these assays are publicly available (e.g., through the trust synthetic state)  Publicly available (e.g., through the trust synthetic and skin), curpal generated. Exemple posterated a synthetic state of the trust synthetic state of the seasy is made if the seasy of the seasy of the seasy of the seasy of the seasy should from Syran and the state of the seasy should from Syran and the state of the seasy should from Syran and the state of the seasy should from Syran and the state of the seasy should from Syran and the state of the seasy should from Syran and season should be should be sometimed by the season of species and glucases and species of the season of support the s | 462 Problation of RANTISS in cuddictain cells (cach as human unablical vein endobletial cells (HUVEC)) |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPSH53                                                                                                |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly perferred embodiment of<br>the invention includes a method for<br>simulating (e.g., increasing) MCP-1<br>doction, An allemative highly<br>preferred embodiment of the<br>invention includes a method for<br>inhibiting (e.g., reducing) MCP-1<br>production. A highly preferred                      |
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| cells. Such assays that may be used mannimum condulatory activity of pulpoperdise of the invention (including antibodies and agoniss or amanoniss of the invention) include the assays disclosed in Minglia et al. Biomodeana Screening 4:193-294 (1999), Rowland et al., 15 mmbodies: a practical approach? Chapter 6:183-160 (2000), Coosti et al., Science 270(524); 181-1816 (1995), and Robinson et al., (2010 Exp. 2010 Ex | MCP-1 PAAT. Assays for immunemodulatory proteins that are produced by a large variety of cells and ext to induce chemoratis and act to induce chemoratis and activation of monocytes and T cells are well known in the art and may be used to routinely modified to assess the ability of polypeptides of the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Production of MCP-1                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 463                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPSP01                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 59                                                                                                                                                                                                                                                                                                            |

| invention (including authodis and agonists or antaqonists of the immunocoldulation, induced immunocoldulation, induced immunocoldulation, induced immunocoldulation, induced induced in services of incremonosity and including seasy patents of the immunocoldulation of proteins evaluate the production of proteins evaluate the production of monocycle activation of monocycle and the activation of monocycle and influential and influe | infections disciplent (e.g. an infection (e.g. an infection e.g. and minderton is disciplent (e.g. and murdur—functions Disease").  Additional lightly preferred Additional lightly preferred inflammation and inflammation growth of the control of t |
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| Chapter 61/824 (2000).  Statington and Evermin, JR (Coll) and Verbasselt et al., Jimmunol 1882 2919-2925 (1997), the contents of each of which are been in corporated by reference in its enteroy. Human doublise cells had now been sugasty may be tassisted to those sugasty may be tassist and the chapter of the contents of each of which are been in the cell in the content of the contents. The contents of which are been in the art. Human development of the contents of sicked the contents of the sicked t | arthritis, AlDs, graunlomanous arthritis, AlDs, graunlomanous arthritis, AlDs, graunlomanous seases, inflammanor bowed disease, sepsis, neutrophilis, popriorisis, supprecision of immune reactions to transplanted organs and tissues, hemophilis, diebes mellins, emotophilis, memiginis (wadernal and allergy. Preferred infloations are seculted below united or services below made or services below made or services. "Hypermolliferative Disorders").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| the high preferred indications include neopleans and cancers, such as, leavening, by propleans, propriet and cancers, such as, leng-clothy parteration, bears, lung-clothy parteration, esoplangeal, sommen, bearin, liver, esoplangeal, sommen, bearin, liver, esoplangeal, sommen, bearin, liver, indications include being in indications include being in consplastic conditions, such as, for neoplastic conditions, such as, for any example, hyporphissia, metaphissia, and of vivisionism. | heighty preferred indication is inhighty preferred indications in additional highly preferred indication is a complication associated with the preferred indication is a complication associated with the disheves (e.g., dishetic retinopathy, iditary disease (e.g., treal infature, traphropathy and the complication of the company of the complication of the company of |
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| cytokines, initiate and upogulate T cell proliferation and functional activities.                                                                                                                                                                                                                                                                                                                                                                                                                  | insulin are well-known in the art and meaning secretion of insulin are well-known in the art and meaning when be used or noninchy modified to assess the ability of polyperlides of the invention of the bylyperlides of the invention of submitted insulin secretion. For example, insulin secretion is example, insulin secretion for summlate insulin secretion for summlate insulin secretion from pancreatic deep list supergulated by glutose and also by octain proteins/peptides, and elist supergulated by glutose and also by octain proteins/peptides, and calls of the supergulation is sky component in diabetes. Exemplary sassys that may polyperlides of the invention of insulin secretion (from pancreatic cells) by polyperlides of the invention include assays disclosed in: Shimian, III, et al. Landon, I, 47(3):216.9 (2000); Salapande, AM, et al., Mol. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | IDPSP01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 65                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Sel, 865,441 (1998), Gaban, L.K.  et al., 1 Biol Chem, 27 (198) Gaba, L.K.  Journal of Biomolecular Secusing, 27 (1996) and, Minglis S et. al., Journal of Biomolecular Secusing, 27 (1996) and A Minglis S et. al., Journal of Biomolecular Secusing, 27 (1996), and A Minglis S et. al., Journal of Biomolecular Secusing, 27 (1996), and a mortal so of the seasys are public evolution to the seasys are public available (e.g., Invogal he ATCC) and or may be rounded by generated. Examplary presented Examplary Secusion, Secusion Biomolecular Secusion and Complex Secusion S | Sci. 1860. Chem. 1.X.  20 (1990) and Aminghi Sci. al.  Journal of Biomolecular Screening.  41 (1922) dand, Minghi Sci. al.  Journal of Biomolecular Screening.  41 (1922) dand, Minghi Sci. al.  Journal of Biomolecular Screening.  41 (1922) day, and Minghi Sci. al.  Journal of Biomolecular Screening.  41 (1922) day, and Minghi Sci. al.  Journal of Biomolecular Screening.  41 (1922) day, and Minghi Sci. al.  Journal of Biomolecular Screening.  Barcanic cells that may be used searched in the "Infectious and planyters" be used according to these assays of modern that of the mingh proferred indication is obesity to be used according to these assays of modern that of the mingh proferred indications are cells carpeter is failth, which is similated by glucose and glucose a | signal transduction that regulate cell the invention includes as method for signal transduction that regulate cell the invention includes as method for method for the cell cowen in the eart and may be a remediatent of the invention the ability of hosperques or the cell cell cell cell cell cell cell ce |
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| HDPSP54 464                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Soc, 86524 14 (1998), the contents of the cont | Ж                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPSP54 464                                                                                                                                                                                                                                                                                                    |

| _ | apoptosis. Exemplary assays for             | proliferation. An alternative highly    |
|---|---------------------------------------------|-----------------------------------------|
|   | JNK kinase activity that may be used        | preferred embodiment of the             |
|   | or routinely modified to test JNK           | invention includes a method for         |
|   | kinase-induced activity of                  | the                                     |
|   | polypeptides of the invention               | proliferation. A highly                 |
|   | (including antibodies and agonists or       | preferred embodiment of the             |
|   | antagonists of the invention) include       | invention includes a method for         |
|   | the assays disclosed in Forrer et al.,      | stimulating apoptosis of endothelial    |
|   | Biol Chem 379(8-9):1101-1110                | cells. An alternative highly preferred  |
|   | (1998); Gupta et al., Exp Cell Res          | embodiment of the invention             |
|   | 247(2): 495-504 (1999); Kyriakis            | includes a method for inhibiting        |
|   | JM, Biochem Soc Symp 64:29-48               | apoptosis of endothelial cells. A       |
|   | (1999); Chang and Karin, Nature             | highly preferred embodiment of the      |
|   | 410(6824):37-40 (2001); and Cobb            | invention includes a method for         |
|   | MH, Prog Biophys Mol Biol 71(3-             | stimulating endothelial cell            |
|   | 4):479-500 (1999); the contents of          | activation. An alternative highly       |
|   | each of which are herein                    | preferred embodiment of the             |
|   | incorporated by reference in its            | invention includes a method for         |
|   | entirety. Endothelial cells that may        | inhibiting the activation of and/or     |
|   | be used according to these assays are       | inactivating endothelial cells.         |
|   | publicly available (e.g., through the       | A highly preferred embodiment of        |
|   | ATCC <sup>TM</sup> ). Exemplary endothelial | the invention includes a method for     |
|   | cells that may be used according to         | stimulating angiogenisis. An            |
|   | these assays include human umbilical        | alternative highly preferred            |
|   | vein endothelial cells (HUVEC),             | embodiment of the invention             |
|   | which are endothelial cells which           | includes a method for inhibiting        |
|   | line venous blood vessels, and are          | angiogenesis. A highly preferred        |
|   | involved in functions that include,         | embodiment of the invention             |
|   | but are not limited to, angiogenesis,       | includes a method for reducing          |
|   | vascular permeability, vascular tone,       | cardiac hypertrophy. An alternative     |
|   | and immune cell extravasation.              | highly preferred embodiment of the      |
|   |                                             | invention include a method for          |
|   |                                             | inducing cardiac hypertrophy.           |
|   |                                             | Highly preferred indications include    |
|   |                                             | neoplastic diseases (e.g., as described |
|   |                                             | below under "Hyperproliferative         |
|   |                                             | Disorders ), and disorders of the       |

| Car      | cardiovascular system (e.g., heart                                |
|----------|-------------------------------------------------------------------|
| dia high | hypertension, aortic stenosis,                                    |
| Cat      | cardiomyopathy, valvular                                          |
| S.C.     | dysfunction, atherosclerosis and                                  |
| ath      | atherosclerotic vascular disease,                                 |
| dia      | diabetic nephropathy, intracardiac                                |
| shu      | shunt, cardiac hypertrophy,                                       |
| my       | myocardial infarction, chronic<br>hemodynamic overload, and/or as |
| sap      | described below under                                             |
| <u>~</u> | "Cardiovascular Disorders").                                      |
| High     | Highly preferred indications include                              |
| car      | cardiovascular, endothelial and/or                                |
| ang      | angiogenic disorders (e.g., systemic                              |
| dis      | disorders that affect vessels such as                             |
| dia      | diabetes mellitus, as well as diseases                            |
| l Jo     | of the vessels themselves, such as of                             |
| the      | the arteries, capillaries, veins and/or                           |
| lyn      | lymphatics). Highly preferred are                                 |
| pui      | indications that stimulate                                        |
| ang      | angiogenesis and/or                                               |
| car      | cardiovascularization. Highly                                     |
| aud      | preferred are indications that inhibit                            |
| ang      |                                                                   |
| car      | cardiovascularization. Highly                                     |
| aud      | preferred indications include                                     |
| ant      | antiangiogenic activity to treat solid                            |
| tun      | tumors, leukemias, and Kaposi"s                                   |
| san      | sarcoma, and retinal disorders.                                   |
| High     | Highly preferred indications include                              |
| Dec .    | neoplasms and cancer, such as,                                    |
| Ka       | Kaposi"s sarcoma, hemangioma                                      |
| (ca      | (capillary and cavernous), glomus                                 |
| tun      | tumors, telangiectasia, bacillary                                 |
| July 1   | anatomatoria                                                      |

| _ |  | hemangioendothelioma,                  |
|---|--|----------------------------------------|
|   |  | angiosarcoma,                          |
|   |  | haemangiopericytoma,                   |
|   |  | lymphangioma, lymphangiosarcoma.       |
|   |  | Highly preferred indications also      |
|   |  | breast, ling, colon, pancreatic.       |
|   |  | esophageal, stomach, brain, liver,     |
|   |  | and urinary cancer. Preferred          |
|   |  | indications include benign             |
|   |  | dysproliferative disorders and pre-    |
|   |  | neoplastic conditions, such as, for    |
|   |  | example, hyperplasia, metaplasia,      |
|   |  | and/or dysplasia. Highly               |
|   |  | preferred indications also include     |
|   |  | arterial disease, such as,             |
|   |  | atherosclerosis, hypertension,         |
|   |  | coronary artery disease,               |
|   |  | inflammatory vasculitides,             |
|   |  | Reynaud's disease and Reynaud's        |
|   |  | phenomenom, aneurysms, restenosis;     |
|   |  | venous and lymphatic disorders such    |
|   |  | as thrombophlebitis, lymphangitis,     |
|   |  | and lymphedema; and other vascular     |
|   |  | disorders such as peripheral vascular  |
|   |  | disease, and cancer. Highly            |
|   |  | preferred indications also include     |
|   |  | trauma such as wounds, burns, and      |
|   |  | injured tissue (e.g., vascular injury  |
|   |  | such as, injury resulting from balloon |
|   |  | angioplasty, and atheroschlerotic      |
|   |  | lesions), implant fixation, scarring,  |
|   |  | ischemia reperfusion injury,           |
|   |  | rheumatoid arthritis, cerebrovascular  |
|   |  | disease, renal diseases such as acute  |
|   |  | renal failure, and osteoporosis.       |
|   |  | Additional highly preferred            |

|         |     |                           |                                       | indications include stroke, graft                            |
|---------|-----|---------------------------|---------------------------------------|--------------------------------------------------------------|
|         |     |                           |                                       | rejection, diabetic or other<br>retinonathies thrombotic and |
|         |     |                           |                                       | coagulative disorders, vascularitis,                         |
|         |     |                           |                                       | lymph angiogenesis, sexual                                   |
|         |     |                           |                                       | disorders, age-related macular                               |
|         |     |                           |                                       | degeneration, and treatment                                  |
|         |     |                           |                                       | /prevention of endometriosis and                             |
|         |     |                           |                                       | related conditions. Additional highly                        |
|         |     |                           |                                       | preferred indications include                                |
|         |     |                           |                                       | fibromas, heart disease, cardiac                             |
|         |     |                           |                                       | arrest, heart valve disease, and                             |
|         |     |                           |                                       | vascular disease. Preferred                                  |
|         |     |                           |                                       | indications include blood disorders                          |
|         |     |                           |                                       | (e.g., as described below under                              |
|         |     |                           |                                       | "Immune Activity", "Blood-Related                            |
|         |     |                           |                                       | Disorders", and/or "Cardiovascular                           |
|         |     |                           |                                       | Disorders"). Preferred indications                           |
|         |     |                           |                                       | include autoimmune diseases (e.g.,                           |
|         |     |                           |                                       | rheumatoid arthritis, systemic lupus                         |
|         |     |                           |                                       | erythematosis, multiple sclerosis                            |
|         |     |                           |                                       | and/or as described below) and                               |
|         |     |                           |                                       | immunodeficiencies (e.g., as                                 |
|         |     |                           |                                       | described below). Additional                                 |
|         |     |                           |                                       | preferred indications include                                |
|         |     |                           |                                       | inflammation and inflammatory                                |
|         |     |                           |                                       | disorders (such as acute and chronic                         |
|         |     |                           |                                       | inflammatory diseases, e.g.,                                 |
|         |     |                           |                                       | inflammatory bowel disease and                               |
|         |     |                           |                                       | Crohn's disease), and pain                                   |
|         |     |                           |                                       | management.                                                  |
| HDPSP54 | 464 | Regulation of apoptosis   | Caspase Apoptosis. Assays for         | A highly preferred indication is                             |
|         |     | in pancreatic beta cells. | caspase apoptosis are well known in   | diabetes mellitus. An                                        |
|         |     |                           | the art and may be used or routinely  | additional highly preferred indication                       |
|         |     |                           | modified to assess the ability of     | is a complication associated with                            |
|         |     |                           | polypeptides of the invention         | diabetes (e.g., diabetic retinopathy,                        |
|         |     |                           | (including antibodies and agonists or | diahetic nenhmnathy kidney disease                           |

| antagonists of the invention) to       | (e.g., renal failure, nephropathy      |
|----------------------------------------|----------------------------------------|
| promote caspase protease-mediated      | and/or other diseases and disorders as |
| apoptosis. Apoptosis in pancreatic     | described in the "Renal Disorders"     |
| beta is associated with induction and  | section below), diabetic neuropathy,   |
| progression of diabetes. Exemplary     | nerve disease and nerve damage         |
| assays for caspase apoptosis that may  | (e.g., due to diabetic neuropathy),    |
| be used or routinely modified to test  | blood vessel blockage, heart disease,  |
| capase apoptosis activity of           | stroke, impotence (e.g., due to        |
| polypeptides of the invention          | diabetic neuropathy or blood vessel    |
| (including antibodies and agonists or  | blockage), seizures, mental            |
| antagonists of the invention) include  | confusion, drowsiness, nonketotic      |
| the assays disclosed in: Loweth, AC,   | hyperglycemic-hyperosmolar coma,       |
| et al., FEBS Lett, 400(3):285-8        | cardiovascular disease (e.g., heart    |
| (1997); Saini, KS, et al., Biochem     | disease, atherosclerosis,              |
| Mol Biol Int, 39(6):1229-36 (1996);    | microvascular disease, hypertension,   |
| Krautheim, A., et al., Br J Pharmacol, | stroke, and other diseases and         |
| 129(4):687-94 (2000); Chandra J, et    | disorders as described in the          |
| al., Diabetes, 50 Suppl 1:S44-7        | "Cardiovascular Disorders" section     |
| (2001); Suk K, et al., J Immunol,      | below), dyslipidemia, endocrine        |
| 166(7):4481-9 (2001); Tejedo J, et     | disorders (as described in the         |
| al., FEBS Lett, 459(2):238-43          | "Endocrine Disorders" section          |
| (1999); Zhang, S., et al., FEBS Lett,  | below), neuropathy, vision             |
| 455(3):315-20 (1999); Lee et al.,      | impairment (e.g., diabetic retinopathy |
| FEBS Lett 485(2-3): 122-126 (2000);    | and blindness), ulcers and impaired    |
| Nor et al., J Vasc Res 37(3): 209-218  | wound healing, and infection (e.g.,    |
| (2000); and Karsan and Harlan, J       | infectious diseases and disorders as   |
| Atheroscler Thromb 3(2): 75-80         | described in the "Infectious           |
| (1996); the contents of each of which  | Discases" section below, especially    |
| are herein incorporated by reference   | of the urinary tract and skin), carpal |
| in its entirety. Pancreatic cells that | me a                                   |
| may be used according to these         | contracture). An additional            |
| assays are publicly available (e.g.,   | highly preferred indication is obesity |
| through the ATCCTM) and/or may be      | and/or complications associated with   |
| routinely generated. Exemplary         | obesity. Additional highly preferred   |
| pancreatic cells that may be used      | indications include weight loss or     |
| according to these assays include      | alternatively, weight gain.            |
| RIN-m. RIN-m is a rat adherent         | Aditional highly preferred             |

| 464 | Intercente peta cell institutora cell intercente verved from 1 radiation radiación polypeptide homonos, and produce polypeptide homonos, and produce instituti, somosantina de possibly glucagon. A TTC # (R&L.2077 Chick et al. Proc. Marl. 1977 P4828, Act es il. Proc. Marl. 1978 P4828, Act es il. Proc. Marl. 1978 P4828, Act es il. Proc. Marl. 1978 P4828, Act es il. Proc. Proc. Proc. Marl. 1978 P4828, Act es il. Proc. Proc. Marl. 1978 P4828, Act es il. Proc. Proc. P | 9 g g | indications are complications associated with insulin resistance.  Highly preferred indications include a great and statement of the preferred indications include highly preferred indications include in the preferred indications include in the preferred indications include in the preferred indications include (e.g., as described below under fee, as described below under Related Disorders'), autoimmune Related Disorders', autoimmune Systemic lipius cryderantosis, systemic lipius cryderantosis, systemic lipius cryderantosis, activities as decrosis in the preferred programment of the preferred in the preferred prefe |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | may be used or notunely monthed to may be used on the worthout of clucking agonists or antegonists of the mortion (including agonists or antegonists of the invention) to modulate LL-10 production and/or T-sell proliferation include, for example, assays such as disclassed and/or evide in Robinson. As a sell and the sell disclassed the hard public 56 (49, 356 - 456 (2000), and Cohar, or all, "T-1 behave Tupe 2 cell directed the neary for ashims" Pharmacology & Transpatures & 187 195 (2000), the contrasts of each of which are the bent in hospotated by reference in their entriesy. Exempling cells that                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |       | undurde as destrate below), immunodeficiencie (e.g., as describe de budy, bosting I T cell- nodianed immune response, and immune response, and immune response.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | A highly preferred emboliment of the invention includes a method est estimating adjuspecyce proliferation. An alternative highly preferred emboliment of the invention includes a method for inhibiting adjuspecyce proliferation.  A highly preferred emboliment of the invention includes a method for inhibiting adjuspecyce proliferation.  An alternative bighly preferred includes a method for inhibiting includes a method for inhibiting includes a method for inhibiting highly preferred emboliment of the invention includes a method for inhibiting adjuspecyce differentiation.  A highly preferred emboliment of the invention includes a method for invention includes in method for intervention for the invention includes in method for invention includes in method for intervention for the invention includes in method for intervention includes in method for interve |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| may be used according to these<br>seasys induch Ch Cedis. LI.10<br>secreted from Th2 cells may be<br>measured as a marker or Th2 cell<br>activation. Th2 cells are a class of<br>T cells that secrete LL4, LL10, LL13,<br>La and L16, Pactors that induce<br>differentiation and activation of Th2<br>cells play a major role in the<br>initiation and publogenesis of allergy<br>initiation and publogenesis of allergy<br>cells are generated via in vitro enture<br>under Th2 polarizing conditions<br>under Th2 polarizing conditions<br>under Th2 polarizing conditions<br>sugge peripheral blood lymphocytes<br>isolated from cord blood. | the man easy, for cumple at IRI-1 kinnes easy, for cumple at IRI-1 kinnes easy, for the Ke spall measuration that regulate cell proliferation of differentiation are well known in the art and may be used or routinely modified to assess the ability of pohypeptides of the reviewing of the behing ambodifies and agonisis or anagousis of the think cell proliferation, activation, and the complete and agonise or managous seasys for ERK kinnes entropy that may be used to routinely modified to test ERK kinnes entropy that may be used pohyperidics of the invention of pohyperidics of the invention including amploties and agoniss or anagonists of the invention included controls and agonis or anagonists of the invention included as any decouls for the assay disclosed in former et al., Biol Chem 279(8-9); 110:1110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Adrivation of Agraviton of Signaling Pathway Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | новуна                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| adipocytes. Highly preferred indications include endocrine               | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, |
|--------------------------------------------------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|
| 107(2):126-132 (1999); Kyriakis JM,<br>Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |
|                                                                          |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |
|                                                                          |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     | _                                     |
|                                                                          |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     | _                                     |

|  |  | stroke, innotence (e.g., due to        |
|--|--|----------------------------------------|
|  |  | dishetic neuronathy or blood vessel    |
|  |  | blockage) saigness mental              |
|  |  | confusion decursings nonfatotic        |
|  |  | contusion, arowaniess, nonvetour       |
|  |  | hyperglycemic-hyperosmolar coma,       |
|  |  | cardiovascular disease (e.g., heart    |
|  |  | disease, atherosclerosis,              |
|  |  | microvascular disease, hypertension,   |
|  |  | stroke, and other diseases and         |
|  |  | disorders as described in the          |
|  |  | "Cardiovascular Disorders" section     |
|  |  | below), dyslipidemia, endocrine        |
|  |  | disorders (as described in the         |
|  |  | "Endocrine Disorders" section          |
|  |  | below), neuropathy, vision             |
|  |  | impairment (e.g., diabetic retinopathy |
|  |  | and blindness), ulcers and impaired    |
|  |  | wound healing, infection (e.g.,        |
|  |  | infectious diseases and disorders as   |
|  |  | described in the "Infectious           |
|  |  | Diseases" section below (particularly  |
|  |  | of the urinary tract and skin). An     |
|  |  | additional highly preferred indication |
|  |  | is obesity and/or complications        |
|  |  | associated with obesity. Additional    |
|  |  | highly preferred indications include   |
|  |  | los                                    |
|  |  | gain. Additional highly                |
|  |  | preferred indications are              |
|  |  | complications associated with insulin  |
|  |  | resistance. Additional highly          |
|  |  | preferred indications are disorders of |
|  |  | the musculoskeletal systems            |
|  |  | including myopathies, muscular         |
|  |  | dystrophy, and/or as described         |
|  |  | herein. Additional highly              |
|  |  | preferred indications include,         |

| hyperension, coronary artery desires, chainly asser, despitories, gallstones, ostooartiritis, degenerative arthritis, esconditistis, degenerative arthritis, degenerative arthritis, and kidney diseases or disorders, and kidney diseases or disorders, and therend indications include neoplasms and cancer, such as, purporns, telestration and betains and the colon, and kidney amore. Additional probabilistic lung, melanoma, prostate, lung, melanoma, prostate diseason melant filipity preferred indications include bengin preferred indications include bengin preferred indications include bengin preferred indications, such as, for neoplastic conditions, such as, for neoplastic conditions, such as, for neoplastic conditions, such as, for endication despitation, and or despitation. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | experie Assay. construct contains<br>regulatory and coding sequence of<br>sequence of the contains and coding<br>enzyme in the cholesterol<br>enzyme in the cholesterol<br>segment of the cholesterol<br>at J. Bal. Chem. 568;1281, et al.<br>12824 (993), the contents of which<br>are brief into opportant by reference<br>in its entirety. Cells were treated<br>with SIO supermanias, and SIOAT<br>enrichty was measured after 72 hours<br>earthorias et al., science,<br>209;497-9 (1980), the contents of<br>the contains of the contents of<br>the contents of the contents of the contents of the<br>reference in its entirety. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | publicio of stalene<br>synthesis gene<br>transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | нрупн26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly                 | preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the inventor includes a method for similaring adioocare differentiation.                                                     | An alternative highly preferred<br>embodiment of the invention<br>includes a method for inhibiting<br>adjrocyte differentiation. A<br>adjrocyte differentiation. A<br>ladjuly preferred embodiment of the<br>invention includes a method for | adipocyte activation. An alternative adipocyte activation. An alternative invention in the property activation and activation and activation includes a method for invention includes a method for invention includes a method for infinition gree activation of (e.g., altituding the activation of (e.g., altituding the activation of the activation of the activation of the activation of the activation and activation and activation and activation and activation and activation activation and activation activation and activation and activation and activation activation activation and activation activation activation and activation and activation activation and activation activation and activation and activation activation activation and activation activation and activation activation activation and activation act | Highly preferred indications also middle properties and the properties are seen to the properties and the properties and the properties are seen to the properties in the properties and the properties in the properties and the properties are properties and the properties and the properties are properties are properties and the properties are properties are properties and the properties are properties and the properties are properties and the properties are properties are properties and the properties are properties and properties are |
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| Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation | are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to rounouse or inhibit cell invention) to rounouse or inhibit cell | proliferation, activation, and<br>differentiation. Exemplary assays for<br>ERK kinase activity that may be used<br>or routinely modified to test ERK<br>for souther activity of<br>polypoptides of the invention                             | viciniting ambidus and agomiss or antiquosis of the invention) included as soys disclosed in Forar et al., Biol Chem 379(8-9); 101-110 (1998), Le Mutand-Brusell Y, Exp Clin Endocrinol Dirickes and Clin Endocrinol Dirickes (1999), Kyaika (1999), Kyaika Mangoli, Shang and Karin Mangoli, Shang and Karin Mangoli, Oloma and Canal Andreas and  | MIT, Prog. Bisophys Mol. Bat 71(2), 4747-5200 (1992), the contents of each of which are breezin component by reference in its entirety. Mones enhoyers cells that may be used according to these assays are publicly available (e.g., mough the Archive and a supplicity of the property of the property of the property of the Archive and a supplicity of the Archive and a supplicity of the Archive and a supplicity of the Archive and th |
| Activation of<br>Adipocyte ERK<br>Signaling Pathway                                                                                             |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 466                                                                                                                                             |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HDPUW68                                                                                                                                         |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 62                                                                                                                                              |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| adhe    | adherent mouse preadipocyte cell<br>line that is a continuous substrain of | "Cardiovascular Disorders", and/or<br>"Blood-Related Disorders", immine |
|---------|----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| 313     | 3T3 fibroblast cells developed                                             | disorders (e.g., as described below                                     |
| thro    | through clonal isolation and undergo                                       | under "Immune Activity"), neural                                        |
| apr     | a pre-adipocyte to adipose-like                                            | disorders (e.g., as described below<br>under "Neural Activity and       |
| diff    | differentiation conditions known in                                        | Neurological Diseases"), and                                            |
| the art | art.                                                                       | infection (e.g., as described below                                     |
|         |                                                                            | under "Infectious Disease").                                            |
|         |                                                                            | A highly preferred indication is                                        |
|         |                                                                            | diabetes mellitus. An additional                                        |
|         |                                                                            | highly preferred indication is a                                        |
|         |                                                                            | complication associated with                                            |
|         |                                                                            | diabetes (e.g., diabetic retinopathy,                                   |
|         |                                                                            | diabetic nephropathy, kidney disease                                    |
|         |                                                                            | (e.g., renal failure, nephropathy                                       |
|         |                                                                            | and/or other diseases and disorders as                                  |
|         |                                                                            | described in the "Renal Disorders"                                      |
|         |                                                                            | section below), diabetic neuropathy,                                    |
|         |                                                                            | nerve disease and nerve damage                                          |
|         |                                                                            | (e.g., due to diabetic neuropathy),                                     |
|         |                                                                            | blood vessel blockage, heart disease,                                   |
|         |                                                                            | stroke, impotence (e.g., due to                                         |
|         |                                                                            | diabetic neuropathy or blood vessel                                     |
|         |                                                                            | blockage), seizures, mental                                             |
|         |                                                                            | confusion, drowsiness, nonketotic                                       |
|         |                                                                            | hyperglycemic-hyperosmolar coma,                                        |
|         |                                                                            | cardiovascular disease (e.g., heart                                     |
|         |                                                                            | disease, atherosclerosis,                                               |
|         |                                                                            | microvascular disease, hypertension,                                    |
|         |                                                                            | stroke, and other diseases and                                          |
|         |                                                                            | disorders as described in the                                           |
|         |                                                                            | "Cardiovascular Disorders" section                                      |
|         |                                                                            | below), dyslipidemia, endocrine                                         |
|         |                                                                            | disorders (as described in the                                          |
|         |                                                                            | "Endocrine Disorders" section                                           |
|         |                                                                            | below), neuropathy, vision                                              |

|  | 1   | impairment (e.g., diabetic retinopathy  |
|--|-----|-----------------------------------------|
|  | -   | and blindness), ulcers and impaired     |
|  | 2   | wound healing, infection (e.g.,         |
|  | -   | infectious diseases and disorders as    |
|  | -0  | described in the "Infectious            |
|  | 1   | Diseases" section below (particularly   |
|  |     | of the urinary tract and skin). An      |
|  |     | additional highly preferred indication  |
|  |     | is obesity and/or complications         |
|  | 80  | associated with obesity. Additional     |
|  |     | highly preferred indications include    |
|  | _   | weight loss or alternatively, weight    |
|  |     | gain. Additional highly                 |
|  | 14  | preferred indications are               |
|  | -   | complications associated with insulin   |
|  |     | resistance. Additional highly           |
|  | 1   | preferred indications are disorders of  |
|  |     | the musculoskeletal systems             |
|  | ·   | including myopathies, muscular          |
|  | -5  | dystrophy, and/or as described          |
|  |     | herein. Additional highly               |
|  |     | preferred indications include,          |
|  |     | hypertension, coronary artery           |
|  | 9   | disease, dyslipidemia, gallstones,      |
|  |     | osteoarthritis, degenerative arthritis, |
|  |     | eating disorders, fibrosis, cachexia,   |
|  |     | and kidney diseases or disorders.       |
|  |     | Preferred indications include           |
|  | T . | neoplasms and cancer, such as,          |
|  | _   | lymphoma, leukemia and breast,          |
|  | •   | colon, and kidney cancer. Additional    |
|  |     | preferred indications include           |
|  | н   | melanoma, prostate, lung,               |
|  |     | pancreatic, esophageal, stomach,        |
|  |     | brain, liver, and urinary cancer.       |
|  |     | Highly preferred indications include    |
|  | _   | ipomas and liposarcomas. Other          |

| preferred indications include benign dysproliferative disorders and prenoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                                                                                                                                               | transacyjnen the activation of transacyjnen to the Serum Response Element (SRE) are well-mown in the art and may be used or routinely modified to assess the amount of the miveration (teichding amphodies and modified to assess the miveration) to regulate the serum reservation to regulate the serum reservation to regulate the serum rescription to regulate the serum reservation to genes involved in expression of genes involved in transacription through the SRE that mixer produced the preservation of the polyperpides of the framention (clumbing sundreids and agoniss or antagoniss of the measured including analysis of the pulled and Malin, Methods in Bregger et al., Fore Natl Acad Sci. 10 (1993); Cullien and Malin, Methods in Bregger et al., Fore Natl Acad Sci. 10 (1993); Cullien and Malin, Methods in Bregger et al., Prov. Natl Acad Sci. 10 (1993); Cullien and Malin, Methods in the Malin are herein incorporated by which are herein incorporated by ATCCC <sup>30</sup> . Exempley                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                               | Treascription though security of the security |
|                                                                                                                                                               | 999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                               | HDPUW68                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                               | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                                                   | CTLL cell line, which is an IL-2 dependent suspension culture of T cells with eyotaonic activity. | below under "Hyperpoliferative products" of the growth of |
|----|---------|-----|---------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 62 | HDPUW68 | 466 | Stimulation of Calcium<br>Flux in pancreatic beta | Assays for measuring calcium flux are well-known in the art and may be                            | under "Infectious Disease"). A highly preferred indication is diabetes mellitus.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|    |         |     | cells.                                            | used or routinely modified to assess                                                              | additional highly preferred indication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| invention) to mobilize calcium. For (e.g., renal failure, nephropathy cannibe, the FLPR assay may be and/or other disease and disorders as used to measure influx of calcium. described in the "Renal Disorders" | <br>llular | ractors can cause an utility of stroke, impotence (e.g., due to calcium, leading to activation of diabetic neuropathy or blood vessel calcium accommence and the control of | functions. Exemplary assays that hyperglycemic-hyperosmolar coma, may be used or routinely modified to cardiovascular disease (e.g., heart | measure calcium flux by disease, atheroselerosis, notynentides of the invention microvascular disease hynertension | antagonists of the invention) include disorders as described in the assessed disclosed in: Satin 1.8 or at 1 "Cardiovascular Disorders" section | Ė | (1995);Mogami H, et al., disorders (as described in the Endocrinology, 136(7):2960-6 "Endocrine Disorders" section | _ | Biochem J, 288 (Pt 3):847-51 impairment (e.g., diabetic retinopathy (1902) and Meats IF et al. Cell and blindheses interes and immaired | 4 | _ | _ | its entirety. Pancreatic cells that may Discases" section below, especially be used according to these assays are of the uniary tract and skin), carnal | <br>ATCC <sup>TM</sup> ) and/or may be routinely contracture). An additional | _ | cells that may be used according to and/or complications associated with |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|---|--------------------------------------------------------------------------------------------------------------------|---|-----------------------------------------------------------------------------------------------------------------------------------------|---|---|---|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---|--------------------------------------------------------------------------|
|                                                                                                                                                                                                                  |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                            |                                                                                                                    |                                                                                                                                                 |   |                                                                                                                    |   |                                                                                                                                         |   |   |   |                                                                                                                                                         |                                                                              |   |                                                                          |

| HITTS are an adherent pilibelial in incidentos incidente vielda loss or cell tire established from Syrian hamser is elect ells transformed with Aditional highly preferred incorporation, and glucosoricitoid exceptions. The cells secrets insulin, which is stimulated by glucoso and supressed by somenosation or glucosoricitoids.  ATTP 608.1-777 Res. Lord and Ashorott. Bookben. 2.19; 447–551. Sanderor et al. Pook. Mark Cal. 177 Res. Lord and Res. Control Experimental Cont | Klimes, sussy, Kinase, sussy, for the invention includes a method for recumple and GSR-5 kinase assay, for the invention includes an enthod for regulate gluose methodism and of all survival.  The standard are well-known in the art method for the invention modified to assess the ability of modified to assess the ability of modified to assess the ability of modified or an embodies of the invention of modified an embodies and agoniss or method for sumitating antipodies and agoniss or massed cell survival.  The standard are successed in the survival of the invention of modified and embodies and agoniss or the invention of modified and embodies of the invention of modified as the survival.  The standard is a survival.  The specific embodiment, skeled muscle end proliferation. In a movemion (including ambiodies and embodies and embodies of the invention modified as the standard and  |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of Skickel Michael Skickel Signalling Pathway Signalling Pa |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 466                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HDPUW68                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| alternative highly preferred embodiment of the invention includes a method for inhibiting mustle cell differentiation, In a most configuration, and a most configuration of the most configuration of th | specinic embodiment, sected miscle<br>cell differentiation is inhibited.<br>Highly preferred indications include<br>disorders of the masculoskeletal<br>system. Preferred indications<br>include reoplastic diseases (e.g., as<br>described below under                   | Hyperpointerative Lissouters ), endocrine dissouters (e.g., as described below under "Endocrine Disouters"), neural disorders (e.g., as described below under "Neural Activity and Neurological | Car<br>Car<br>Car<br>d be | hasses'). A might preferred indeation is dishered a maging preferred and distinguish preferred indeation is dishered seems. The analysis preferred indeation is a complication is a complication of a complication of the property disheric returnpathy, disheric return |
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| of each of which are herein incorporated by reference in its entirely. Rat myoblast cells that may be used according to these assays are matical control of the each the control of the co | punicy availance (e.g., modgin the<br>ATCCPA). Exemplary rat myoblast<br>cells that may be used according to<br>these assays include L6 cells. L6 is<br>an adherent rat myoblast cell line,<br>isolated from primary cultures of rat<br>thigh muscle, that fisses to form | mulmheleated myotubes and strated<br>fibers after culture in differentiation<br>media.                                                                                                          |                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| due to diabetic neuropathy), blood vesse blookag, hent disease, sroke, impotence (e.g., due to diabetic neuropathy or blood vessel                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| blockago), seizures, mental confusion, duwsiness, nonfoseotic hyperglycenii-hypergroniid-noneotic racidovaseular disease (e.g., heart                                                                                                         |
| disease, alterolectorische disease, alterolectorisch, microwesular disease, hypertension, stroke, and other diseases and disearches and disearches as dearnbed in the "Cardiovascular Disearches' section "Cardiovascular Disearches' section |
| helov), Aysindrami, endocrine disorder, Robernhed in the Tradocrine Disorder's esction Pradocrine Disorder's esction Polovy, neuropariny, vision impairment (e.g., diabetic retinopathy and bilindiness), lucers and impaired                 |
| wound bealing infections (e.g., infections dissorters as described in the "Infections as Diseases' section below, especially of the urinary treat and skin), carpal turned syndrome and Disputper's contracture). An additional contracture.  |
| highly preferred indication is obesity and/or completations associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred Additional highly preferred       |
| indications are complications associated with insulin resistance. Additional highly preferred indications are disorded so of the impactions defined in your monthly in musculoskeletal system including                                       |

|         |     |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | androit as described bettern androit as described bettern indication as lighty preferred indications literature in the described preferred indications include: moyalidy, seasons, or ongential cardions allows. Browns fibrours, or ongential cardions either in the desease, cardiac arrest, heart valves disease, tallidy preferred indications include pure partners the preferred indications include beauty classes. Preferred indications include beauty desponditionaries, termi, and livre entered the preferred indications include beauty desponditions, and as, hyperplasia, and or hyperplasia, and or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| HDPWU34 | 467 | Activation of Adipocyce PJ Kinase Signalling Pattway | Kinase assay. Kinase assays, for<br>example in GNE3 assays, for PB<br>kinase signal transduction that<br>regulate glucose remetabolism and cell<br>survival are well-known in the art<br>and may be used or routinely<br>modified to assess the ability of<br>popperdise of the invention<br>of challenging and applying the<br>popperdise of the invention of<br>promote or inhibit glucose<br>promote or inhibit glucose<br>promote or inhibit glucose<br>in the properties of a survival.<br>Exemplary assays for PB kinase<br>Exemplary assays for PB kinase<br>Exemplary assays for PB kinase<br>and the cell PB kinase and the continely<br>modified to set PB kinase changed | On Stabilistics of Control of Stabilistics of Control of Stabilistics of Control of Cont |

| activity  | activity of polypeptides of the        | invention includes a method for        |
|-----------|----------------------------------------|----------------------------------------|
| invention | invention (including antibodies and    | stimulating adipocyte differentiation. |
| agonists  | agonists or antagonists of the         | An alternative highly preferred        |
| invention | invention) include assays disclosed in | embodiment of the invention            |
| Forrer et | Forrer et al., Biol Chem 379(8-        | includes a method for inhibiting       |
| -101:101  | 9):1101-1110 (1998); Nikoulina et      | adipocyte differentiation. Highly      |
| al., Diab | al., Diabetes 49(2):263-271 (2000);    | preferred indications include          |
| and Schr  | and Schreyer et al., Diabetes          | endocrine disorders (e.g., as          |
| 48(8):16  | 48(8):1662-1666 (1999), the contents   | described below under "Endocrine       |
| of each o | of each of which are herein            | Disorders"). Preferred indications     |
| incorpor  | incorporated by reference in its       | include neoplastic diseases (e.g.,     |
| entirety. | entirety. Mouse adipocyte cells that   | lipomas, liposarcomas, and/or as       |
| may be u  | may be used according to these         | described below under                  |
| assays at | assays are publicly available (e.g.,   | "Hyperproliferative Disorders"),       |
| through   | through the ATCCTM). Exemplary         | blood disorders (e.g., hypertension,   |
| mouse ad  | mouse adipocyte cells that may be      | congestive heart failure, blood vessel |
| nsed acc  | used according to these assays         | blockage, heart disease, stroke,       |
| include 3 | include 3T3-L1 cells. 3T3-L1 is an     | impotence and/or as described below    |
| adherent  | adherent mouse preadipocyte cell       | under "Immune Activity",               |
| line that | ine that is a continous substrain of   | "Cardiovascular Disorders", and/or     |
| 3T3 fibra | 3T3 fibroblast cells developed         | "Blood-Related Disorders"), immune     |
| through   | through clonal isolation and undergo   | disorders (e.g., as described below    |
| a pre-adi | a pre-adipocyte to adipose-like        | under "Immune Activity"), neural       |
| conversi  | conversion under appropriate           | disorders (e.g., as described below    |
| different | differentiation conditions known in    | under "Neural Activity and             |
| the art.  |                                        | Neurological Diseases"), and           |
|           |                                        | infection (e.g., as described below    |
|           |                                        | under "Infectious Disease"). A         |
|           |                                        | highly preferred indication is         |
|           |                                        | diabetes mellitus. An                  |
|           |                                        | additional highly preferred indication |
|           |                                        | is a complication associated with      |
|           |                                        | diabetes (e.g., diabetic retinopathy,  |
|           |                                        | diabetic nephropathy, kidney disease   |
|           |                                        | (e.g., renal failure, nephropathy      |
|           |                                        | and/or other diseases and disorders as |
|           |                                        | described in the "Renal Disorders"     |

|  | section below), diabetic neuropathy,   |
|--|----------------------------------------|
|  | nerve disease and nerve damage (e.g.   |
|  | due to diabetic neuropathy), blood     |
|  | vessel blockage, heart disease,        |
|  | stroke, impotence (e.g., due to        |
|  | diabetic neuropathy or blood vessel    |
|  | blockage), seizures, mental            |
|  | confusion, drowsiness, nonketotic      |
|  | hyperglycemic-hyperosmolar coma,       |
|  | cardiovascular disease (e.g., heart    |
|  | disease, atherosclerosis,              |
|  | microvascular disease, hypertension,   |
|  | stroke, and other diseases and         |
|  | disorders as described in the          |
|  | "Cardiovascular Disorders" section     |
|  | below), dyslipidemia, endocrine        |
|  | disorders (as described in the         |
|  | "Endocrine Disorders" section          |
|  | below), neuropathy, vision             |
|  | impairment (e.g., diabetic retinopathy |
|  | and blindness), ulcers and impaired    |
|  | wound healing, infection (e.g.,        |
|  | infectious diseases and disorders as   |
|  | described in the "Infectious           |
|  | Diseases" section below, especially    |
|  | of the urinary tract and skin), carpal |
|  | tunnel syndrome and Dupuytren's        |
|  | contracture). An additional            |
|  | highly preferred indication is obesity |
|  | and/or complications associated with   |
|  | obesity. Additional highly preferred   |
|  | indications include weight loss or     |
|  | alternatively, weight gain.            |
|  | Additional highly preferred            |
|  | indications are complications          |
|  | associated with insulin resistance.    |
|  | Additional highly preferred            |

|    |         |     |                       |                                        | indications are disorders of the        |
|----|---------|-----|-----------------------|----------------------------------------|-----------------------------------------|
|    |         |     |                       |                                        | musculoskeletal systems including       |
|    |         |     |                       |                                        | myopathies, muscular dystrophy,         |
|    |         |     |                       |                                        | and/or as described herein.             |
|    |         |     |                       |                                        | Additional highly preferred             |
|    |         |     |                       |                                        | indications include, hypertension,      |
|    |         |     |                       |                                        | coronary artery disease,                |
|    |         |     |                       |                                        | dyslipidemia, gallstones,               |
|    |         |     |                       |                                        | osteoarthritis, degenerative arthritis, |
|    |         |     |                       |                                        | eating disorders, fibrosis, cachexia,   |
|    |         |     |                       |                                        | and kidney diseases or disorders.       |
|    |         |     |                       |                                        | Highly preferred indications include    |
|    |         |     |                       |                                        | neoplasms and cancer, such as,          |
|    |         |     |                       |                                        | lipoma, liposarcoma, lymphoma,          |
|    |         |     |                       |                                        | leukemia and breast, colon, and         |
|    |         |     |                       |                                        | kidney cancer. Additional highly        |
|    |         |     |                       |                                        | preferred indications include           |
|    |         |     |                       |                                        | melanoma, prostate, lung,               |
|    |         |     |                       |                                        | pancreatic, esophageal, stomach,        |
|    |         |     |                       |                                        | brain, liver, and urinary cancer.       |
|    |         |     |                       |                                        | Other preferred indications include     |
|    |         |     |                       |                                        | benign dysproliferative disorders and   |
|    |         |     |                       |                                        | pre-neoplastic conditions, such as,     |
|    |         |     |                       |                                        | for example, hyperplasia, metaplasia,   |
|    |         |     |                       |                                        | and/or dysplasia.                       |
|    | HDPWU34 | 467 | Activation of         | Assays for the activation of           | Highly preferred indications include    |
| 63 |         |     | transcription through | transcription through the Gamma        | asthma, allergy, hypersensitivity       |
|    |         |     | GAS response element  | Interferon Activation Site (GAS)       | reactions, inflammation, and            |
|    |         |     | in immune cells (such | response element are well-known in     | inflammatory disorders. Additional      |
|    |         |     | as eosinophils).      | the art and may be used or routinely   | highly preferred indications include    |
|    |         |     |                       | modified to assess the ability of      | immune and hematopoietic disorders      |
|    |         |     |                       | polypeptides of the invention          | (e.g., as described below under         |
|    |         |     |                       | (including antibodies and agonists or  | "Immune Activity", and "Blood-          |
|    |         |     |                       | antagonists of the invention) to       | Related Disorders"), autoimmune         |
|    |         |     |                       | modulate gene expression               | diseases (e.g., rheumatoid arthritis,   |
|    |         |     |                       | (commonly via STAT transcription       | systemic lupus erythematosis,           |
|    |         |     |                       | factors) involved in a wide variety of | Crohn"s disease, multiple sclerosis     |

| and/or as described below),          | described below), boosting an        | eosinophil-mediated immune      | response and, alternatively, | suppressing an eosinophil-mediated | immune response.                      |                                       |                                    |                                 |                          |                                     |                                 |                               |                                   |                                         |                             |                               |                                      |                                  |                               |                                      |                                   |                              |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                                |                                     |                            |
|--------------------------------------|--------------------------------------|---------------------------------|------------------------------|------------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|--------------------------|-------------------------------------|---------------------------------|-------------------------------|-----------------------------------|-----------------------------------------|-----------------------------|-------------------------------|--------------------------------------|----------------------------------|-------------------------------|--------------------------------------|-----------------------------------|------------------------------|-------------------------------|---------------------------------------|----------------------------------|-----------------------------------|-----------------------------|-----------------------------------|----------------------------------|---------------------------|-------------------------|------------------------------|-------------------------------|-----------------------------------|--------------------------------|-------------------------------------|----------------------------|
| cell functions. Exemplary assays for | response element that may be used or | routinely modified to test GAS- | response element activity of | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm. Methods in Enzymol | 216:362-368 (1992): Henthorn et al. | Proc Natl Acad Sci USA 85:6342- | 6346 (1988). Matikainen et al | Blood 93(6):1980-1991 (1999): and | mm (/////////////////////////////////// | Henttinen et al., J Immunol | 155(10):4582-4587 (1995); the | contents of each of which are herein | incorporated by reference in its | entirety. Moreover, exemplary | assays that may be used or routinely | modified to assess the ability of | achimomides of the investion | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to | activate or inhibit activation of | immune cells include assays | disclosed and/or cited in: Mayumi | M., "EoL-1, a human cosinophilic | cell line" Leuk Lymphoma; | Jun;7(3):243-50 (1992); | Bhattacharya S, "Granulocyte | macrophage colony-stimulating | factor and interlenkin-5 activate | STAT5 and inchese CIS1 mRNA in | human nerinberal blood eosinoabile" | Am J Respir Cell Mol Biol; |
|                                      |                                      |                                 |                              |                                    |                                       |                                       |                                    |                                 |                          |                                     |                                 |                               |                                   |                                         |                             |                               |                                      |                                  |                               |                                      |                                   |                              |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                                |                                     |                            |
|                                      |                                      |                                 |                              |                                    |                                       |                                       |                                    |                                 |                          |                                     |                                 |                               |                                   |                                         |                             |                               |                                      |                                  |                               |                                      |                                   |                              |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                                |                                     |                            |
|                                      |                                      |                                 |                              |                                    |                                       |                                       |                                    |                                 |                          |                                     |                                 |                               |                                   |                                         |                             |                               |                                      |                                  |                               |                                      |                                   |                              |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                                |                                     |                            |
|                                      |                                      |                                 |                              |                                    |                                       |                                       |                                    |                                 |                          |                                     |                                 |                               |                                   |                                         |                             |                               |                                      |                                  |                               |                                      |                                   |                              |                               |                                       |                                  |                                   |                             |                                   |                                  |                           |                         |                              |                               |                                   |                                |                                     |                            |

| Mar,24(3):312-6 (2001); and, Du J., adapter in interchetin-5 signaling in accomplist's plan (Clear, Cott. 20,275(42):3167-75 (2000); the contents of each of which are therein incorporated by reference in its entirety. Exemplary cells that may entirety. Exemplary cells that may include costangitist I fosionophils are present a proper of immune cell important in the late stage of allergis creation to the late stage of allergis creation. Increases in GAS mediated to answer plan mediate the inflammory resolute or in GAS mediated to answer plan in GAS mediated to answer plan costangiatist is oppetally a result of costangiatist of control and control consequence of interchetin or other CAS mediated to answerption in costangiatist is oppetally a result of consequence of interchetin or other CAS cockine recognor normally a direct consequence of interchetin or other IL3, IL5 or GMCSE). | wassy for the regulation (i.e., sayes) for the regulation (i.e., sayes) for the regulation of cells in vitro are and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess in which the hality of polyperidies of the invention (including antibodies and invention) for including antibodies and invention to regulate viability and partial or present of the invention) to regulate viability and polification of proc-adipose cells and cell lines. For example, the Cell Titter-Goldo Luminescent Cell within Yasay (Puronege Corp., Madison, W. U.SA) can be used to Madison, W. U.SA) can be used to culture based on quantitation of the culture based on quantitation of the |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | infiliration of pragilitation of pragilitation of pragilitation and 373-L1 cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 467                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HDPWU34                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 59                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|    |         |     |                   | ATP present which signals the           |                                  |
|----|---------|-----|-------------------|-----------------------------------------|----------------------------------|
|    |         |     |                   | presence of metabolically active        |                                  |
|    |         |     |                   | cells. 3T3-L1 is a mouse                |                                  |
|    |         |     |                   | preadipocyte cell line. It is a         |                                  |
|    |         |     |                   | continuous substrain of 3T3             |                                  |
|    |         |     |                   | fibroblast cells developed through      |                                  |
|    |         |     |                   | clonal isolation. Cells were            |                                  |
|    |         |     |                   | differentiated to an adipose-like state |                                  |
|    |         |     |                   | before being used in the screen. See    |                                  |
|    |         |     |                   | Green H and Meuth M., Cell 3: 127-      |                                  |
|    |         |     |                   | 133 (1974), which is herein             |                                  |
|    |         |     |                   | incomorated by reference in its         |                                  |
|    |         |     |                   | entinety                                |                                  |
|    | HDPWU34 | 467 | Activation of     | Assays for activation of transcription  |                                  |
| 63 |         |     | Transcription     | are well-known in the art and may be    |                                  |
|    |         |     | •                 | used and routinely modified to assess   |                                  |
|    |         |     |                   | ability of polymentides of the          |                                  |
|    |         |     |                   | aoung or postpopures or are             |                                  |
|    |         |     |                   | invention to inhibit or activate        |                                  |
|    |         |     |                   | transcription. An example of such an    |                                  |
|    |         |     |                   | assay follows: Cells were pretreated    |                                  |
|    |         |     |                   | with SID supernatants or controls for   |                                  |
|    |         |     |                   | 15-18 hours. SEAP activity was          |                                  |
|    |         |     |                   | measured after 48 hours. LS174T is      |                                  |
|    |         |     |                   | an epithelial colon adenocarcinoma      |                                  |
|    |         |     |                   | cell line. Its tumourigenicity in nude  |                                  |
|    |         |     |                   | mice make cell line LS174T a model      |                                  |
|    |         |     |                   | for studies on the mechanism of         |                                  |
|    |         |     |                   | synthesis and secretion of specific     |                                  |
|    |         |     |                   | tumoral markers in colon cancer.        |                                  |
|    |         |     |                   | See, Patan et al., Circ Res, 89(8):732- |                                  |
|    |         |     |                   | 39 (2001), the contents of which are    |                                  |
|    |         |     |                   | herein incomorated by reference in      |                                  |
|    |         |     |                   | its entircty.                           |                                  |
|    | HDPXY01 | 468 | Insulin Secretion | Assays for measuring secretion of       | A highly preferred indication is |
| Ī  |         |     |                   | insulin are well-known in the art and   | diabetes mellitus. An additional |
|    |         |     |                   | may be used or routinely modified to    | highly preferred indication is a |
|    |         |     |                   | assess the ability of polypeptides of   | complication associated with     |
|    |         |     |                   |                                         |                                  |

| diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders a described in the "Renal Disorders" | section below), diabetic neuropathy, nerve disease and nerve diamage (e.g., due to diabetic neuropathy), blood vessel biockage, heart disease, stroke, impotence (e.g., due to         | unactor tentopano y totoco vessors blockago, seztures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperglycemic-hyperglycemic-hyperconolar coma, eachiovascular disease (e.g., heart disease, arberosclerosis, microvascular disease, hypertension, microvascular disease, hypertension, and constructions of the construction of the construc | chemical and property and prope | infections diseases and disorders as infections diseases and disorders as been excited in the "Infections Diseases" section to fow the trainers are and Daylyten's contracture). An additional turnel syndense and Daylyten's contracture). An additional turnel syndense and Daylyten's contracture). An additional turnel syndense and Daylyten's andre complications associated with andrest Additional highly perferred discussion is obesity andrein highly perferred the angle of the perfer and the perfect and the perfer and the perfect and the perfect and the perfer and the perfer and the perfect and the perfect and the perfer and the perfect and the per                                                                                                                                                                                                                                                                               |
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| the invention (including antibodies<br>and agonists or anagonists of the<br>invention) to stimulate insulin<br>secretion. For example, insulin<br>secretion is measured by FMAT       | using anti-rat insulin antibodies. Insulin socretion from penceratic beta cells is upregulated by glucose and also by certain proteins/peptides, and disception is a leey component in | unceed, a season and assist sum tran-<br>be used or routinely modified to test<br>for stimulation of insulin secretion<br>(from pancreatic cells) by<br>polypopties of the invention<br>(including anthodies and agonists or<br>antagonists of the covering) include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | al., Findon; 1, 47(2), 26(4), 9(2000); al., Findon; 4, 47(2), 26(4), 9(2000); al., Findourino; 1, 3(8), 130(4); (1, 9), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1), 9(1),  | 11/9-2.24 (1935), the contrains of<br>each of which is herein incorporated<br>by reference in its entirey.  Pancreatic cells that may be used<br>according to these assays are publicly<br>available (e.g., hrough the ATCCPA)<br>and/or may be routinely generated.  The carrying the processing of the contraints of the con-<br>traints |
|                                                                                                                                                                                       |                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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|                                                                                                                                                                                       |                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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|   |          |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | established from Syrian humserristed cells transformed with SV40. These cells express glueagen, somanostatin, and addition-orthod exergines. The cells secrete insulin, which is cells secrete insulin, which is cells secrete insulin, which is delike a secrete insulin, which is cells secrete insulin, which is cells secrete insulin, which is cell secrete insulin, which is cell secret insulin, which sear and approves day sommersatin or gluecoroticosids. ATTC# CRL-1777 glues for the secrete insulin, which secrete in the cells of the secrete insuling the s                                                                                                                                                                                                                                             | alematively, weight gain. Additional highly preferred indications are orgalications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| 8 | ID/IB/77 | 689 | transcription via Pagalation of transcription via Pagalation of transcription via Pagalation via | transarription through the DMEP<br>transarription through the DMEP<br>transarription through the DMEP<br>the start and may be used or routinely<br>the start and may be used or routinely<br>the start and may be used or routinely<br>published to a start and may be used<br>transarription from the representation to<br>clinical and the constraints of<br>the start and the start and<br>the star | diabetes realitius. Additional highly preferred indications in purpose the property of the compileration in the compileration is neither diabetes realitius. Additional highly perferred indications include compilerations associated diabetes (e.g. diabetic retinopality, diabetic retinopality, idane) diabetic reproposity, kidney diasesses and distorters as described in the 'Renal Distorter's and courted distorters and described in the 'Renal Distorter's and courted distorter to appropriate the entropality in the 'Renal Distorter's and control face, and to diabetic neuropality, blood vessel blockage, heart distorter, importero (e.g., due to diabetic neuropality or blood vessel blockage, heart distorters, and contision, drowsiness, montal contision, drowsiness (e.g., heart distorters) and distorters as ection distorters as described in the Action research and distorters as described in the Action research and Action drows Action and Action drows Action and Action of the ac |

| A highly preferred embodiment of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Caspase Apoptosis. Assays for                         | Endothelial Cell | 470 | HDTDQ23 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|------------------|-----|---------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | under appropriate differentiation culture conditions. |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adipocyte to adipose-like conversion                  |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | isolation. These cells undergo a pre-                 |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | fibroblasts developed through clonal                  |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | continuous substrain of 3T3                           |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | line. Mouse 3T3-L1 cells are a                        |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adherent mouse preadipocyte cell                      |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | mouse 3T3-L1 cell line which is an                    |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | according to these assays include the                 |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Exemplary cells that may be used                      |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and/or may be routinely generated.                    |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | available (e.g., through the ATCC <sup>TM</sup> )     |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | according to these assays are publicly                |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adipocytes that may be used                           |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | entirety. Adipocytes and pre-                         |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | incorporated by reference in its                      |                  |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | contents of each of which is herein                   |                  |     |         |
| associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Enzymol. 216:362-368 (1992), the                      |                  |     |         |
| indications are complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Cullen, B., et al., Methods in                        |                  |     |         |
| gain. Additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | al., Gene 66:1-10 (1988); and,                        |                  |     |         |
| weight loss or alternatively, weight                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Aug 4;275(31):23666-73; Berger, et                    |                  |     |         |
| highly preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | transgenic mice", J Biol Chem. 2000                   |                  |     |         |
| associated with obesity. Additional                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | human GLUT4 promoter in                               |                  |     |         |
| is obesity and/or complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | binding protein that regulates the                    |                  |     |         |
| additional highly preferred indication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | regulatory element and novel DNA                      |                  |     |         |
| of the urinary tract and skin). An                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | "Identification of a 30-base pair                     |                  |     |         |
| Diseases" section below, especially                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Chem, 269(45):28514-21 (1994);                        |                  |     |         |
| described in the "Infectious                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | (2000); Liu, M.L., ct al., J Biol                     |                  |     |         |
| infectious diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | et al., J Biol Chem, 275(21):16323-8                  |                  |     |         |
| wound healing, and infection (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 273(23):14285-92 (1998); Mora, S.,                    |                  |     |         |
| and blindness), ulcers and impaired                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | in Thai, M.V., et al., J Biol Chem,                   |                  |     |         |
| impairment (e.g., diabetic retinopathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | invention) include assays disclosed                   |                  |     |         |
| below), neuropathy, vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | and agonists or antagonists of the                    |                  |     |         |
| THE PARTY OF THE P | the invention (including antibodies                   |                  |     |         |
| "Endocrine Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1.10.10.10.10.10.1                                    |                  |     |         |

| the invention includes a me<br>stimulating endothelial cell<br>An alternative highly prefe<br>embodiment of the invention<br>includes a method for inhit                       | endothelial cell gre preferred embodini invention includes stimulating endoth proliferation. An a preferred embodini invention includes inhibiting endothel                                                                                                                                                            | populeration. A nighty preferred embedianest of the mirration includes a method for sammlating apoptosis of endothelind embediance highly preferred embedianest of the invention including (e.g., includes a method for inhibiting (e.g., includes method for inhibiting (e.g., decreasing) apoptosis of endotheling (e.g., decreasing) apoptosis of endothelind embedianest of the invention embedianest of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| caspase apoptosis are well known in the art and may be used or routirely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or | antigenaiss of the invention) to promote expose protesse-mediated apoptosis. Induction of apoptosis in endobthic leds supporting the vasculature of turnos is associated with tumor regression due to loss of tumor blood supply. Exemples assuss for exspace apoptosis that may assuss for exspace apoptosis that may | to the case of remaining the case of the case of the mineral of the case of the mineral of the case of the case of the mineral of the case of the mineral of the case of the c | (1996), the contents of each of which are therein monoproaded by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., however, and the content of the c |
| Apoptosis                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 99                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|  |  | tumors, telangiectasia, bacillary      |
|--|--|----------------------------------------|
|  |  | angiomatosis,                          |
|  |  | hemangioendothelioma,                  |
|  |  | angiosarcoma,                          |
|  |  | haemangiopericytoma,                   |
|  |  | lymphangioma, lymphangiosarcoma.       |
|  |  | Highly preferred indications also      |
|  |  | include cancers such as, prostate,     |
|  |  | breast, lung, colon, pancreatic,       |
|  |  | esophageal, stomach, brain, liver,     |
|  |  | and urinary cancer. Preferred          |
|  |  | indications include benign             |
|  |  | dysproliferative disorders and pre-    |
|  |  | neoplastic conditions, such as, for    |
|  |  | example, hyperplasia, metaplasia,      |
|  |  | and/or dysplasia. Highly               |
|  |  | preferred indications also include     |
|  |  | arterial disease, such as,             |
|  |  | atherosclerosis, hypertension,         |
|  |  | coronary artery disease,               |
|  |  | inflammatory vasculitides,             |
|  |  | Reynaud's disease and Reynaud's        |
|  |  | phenomenom, aneurysms, restenosis;     |
|  |  | venous and lymphatic disorders such    |
|  |  | as thrombophlebitis, lymphangitis,     |
|  |  | and lymphedema; and other vascular     |
|  |  | disorders such as peripheral vascular  |
|  |  | disease, and cancer. Highly            |
|  |  | preferred indications also include     |
|  |  | trauma such as wounds, burns, and      |
|  |  | injured tissue (e.g., vascular injury  |
|  |  | such as, injury resulting from balloon |
|  |  | angioplasty, and atheroschlerotic      |
|  |  | lesions), implant fixation, scarring,  |
|  |  | ischemia reperfusion injury,           |
|  |  | rheumatoid arthritis, cerebrovascular  |
|  |  | disease, renal diseases such as acute  |

|    |         |     |                         |                                      | renal failure, and osteoporosis.                                 |
|----|---------|-----|-------------------------|--------------------------------------|------------------------------------------------------------------|
|    |         |     |                         |                                      | Additional highly preferred<br>indications include stroke, graft |
|    |         |     |                         |                                      | rejection, diabetic or other                                     |
|    |         |     |                         |                                      | retinopathies, thrombotic and                                    |
|    |         |     |                         |                                      | coagulative disorders, vascularitis,                             |
|    |         |     |                         |                                      | lymph angiogenesis, sexual                                       |
|    |         |     |                         |                                      | disorders, age-related macular                                   |
|    |         |     |                         |                                      | degeneration, and treatment                                      |
|    |         |     |                         |                                      | /prevention of endometriosis and                                 |
|    |         |     |                         |                                      | related conditions. Additional highly                            |
|    |         |     |                         |                                      | preferred indications include                                    |
|    |         |     |                         |                                      | fibromas, heart disease, cardiac                                 |
|    |         |     |                         |                                      | arrest, heart valve disease, and                                 |
|    |         |     |                         |                                      | vascular disease. Preferred                                      |
|    |         |     |                         |                                      | indications include blood disorders                              |
|    |         |     |                         |                                      | (e.g., as described below under                                  |
|    |         |     |                         |                                      | "Immune Activity", "Blood-Related                                |
|    |         |     |                         |                                      | Disorders", and/or "Cardiovascular                               |
|    |         |     |                         |                                      | Disorders"). Preferred indications                               |
|    |         |     |                         |                                      | include autoimmune diseases (e.g.,                               |
|    |         |     |                         |                                      | rheumatoid arthritis, systemic lupus                             |
|    |         |     |                         |                                      | erythematosis, multiple sclerosis                                |
|    |         |     |                         |                                      | and/or as described below) and                                   |
|    |         |     |                         |                                      | immunodeficiencies (e.g., as                                     |
|    |         |     |                         |                                      | described below). Additional                                     |
|    |         |     |                         |                                      | preferred indications include                                    |
|    |         |     |                         |                                      | inflammation and inflammatory                                    |
|    |         |     |                         |                                      | disorders (such as acute and chronic                             |
|    |         |     |                         |                                      | inflammatory diseases, e.g.,                                     |
|    |         |     |                         |                                      | inflammatory bowel disease and                                   |
|    |         |     |                         |                                      | Crohn's disease), and pain                                       |
|    |         |     |                         |                                      | management.                                                      |
| 3  | HDTDQ23 | 470 | Stimulation of Calcium  | Assays for measuring calcium flux    | A highly preferred indication is                                 |
| 99 |         |     | Fiux in pancreatic beta | are well-known in the art and may be | diabetes mellitus. An                                            |
|    |         |     | cells.                  | used or routinely modified to assess | additional highly preferred indication                           |
|    |         |     |                         | the ability of polypeptides of the   | is a complication associated with                                |

| diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" | section below), disbetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy). blood vessel bloodses, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel                 | notacings), sezuraci, inclusi<br>contission, drowsiness, nondeciotic<br>hyperglycemic-hyperosmolar coma,<br>acutiovascular disease (e.g., heart<br>disease, adhenoslerosis,<br>microvascular disease, hypertension,<br>stock, and other diseases and<br>disorders as described in the                                    |                                                                                                                                                                                                                                                                                                                                                                        | returnitus tuesses and usarious as described in the "Infectious as the page and page and the tues and study of the uniony treat and skinly, carry and study treat and page and page and the union synchronic and page and the union synchronic and the union treat and the union treatment. An additional and/or complication associated with and or complications associated with the objects. Additional highly preferred unifications is obesity and or complications associated with the union include weight loss of the page and the union of the un |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the HPR assay may be used to measure influx of calcium.                | Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular existion. Extracellular factors can cause an influx of calcium, leading to activation of calcium, leading to activation of | calcular response ve signating pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure actions that by polypeptides of the invention (modifing amplies and agonisis or anatomistics of the invention) include antagonisis or anatomists of the invention include. | assays distoled in: Suin LS, et al.,<br>Endocrinology, 136(10)(4589-601 (1995); Morgaun II, et al.<br>(1995); Morgaun II, et al.<br>Endocrinology, 136(7):2860-6<br>(1995); Redantdown SB, et al.,<br>Bochen J, 236 (P. 19847-51<br>(1992); and, Mens, JE, et al., Cell<br>Colcium 1990; and, Mens, JE, et al., Cell<br>(1992); All All All All All All All All All Al | (1999), net comments it early on which is better in compounted by reference in settings; Praceratic cells han may be used according to these assays are publicly available (e.g., frontigh the ATCC**) and/or may be routined by ATCC**) and/or may be routined by agreented. Exempling pasteractic cells that may be used according to these assays into the stage as address or entitled IIITT15 Cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                        |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                        |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| alternatively, weight gan,<br>Additional high preferred<br>indications associated with instilln resistance.                                                                                                                                                                                                                                                                                                                                                                                         | A highly preferred indication is diabetes netilities. The additional lighty preferred indication is a complication associated with discussion is a complication associated with discussion of the additional lighty preferred indication is a complication associated with discussion of the additional light proferred indication of the additional light proferred indication reaching and do work discussion and instruct discussion and instruct discussion and nerve discussion and reave discussion and reave discussion in the additional control districts to emerginally or blood vessel bloodings, bear discussion, and conditions, drowsiness, nonethal conditions, drowsiness, nonethal conditions, drowsiness, member of districts to emerginal or on districts of the additional and or discussions, and or discusses, admonstration of discustes and discusses, in through a discussion, cardiovascular discusses, by proferration, cardiovascular discusses, in the Cardiovascular discusses, and discorders as described in the discorders as described in the below, docsting-denting, and control as setting and a discording and a  |
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| ve clel line established from Syrian humater islet cells transformed with Sy40. These cells express glueugon, Syanonssaini, and glueocorticoid receptors. The cells servet einstilling which is simulated by glueose and glueugon and suppressed by somatostain or glueocorticoids. ATTA (Rel. L.TTA) Rels. Lend. AATAC (RLL. TTA) Rels. Lend. Seature et al. Poet. Natl. Acad. Sci. USA 78: 4339-434, 1981. | caspase apoptosis as avey literactions as a consideraction are under homowing the art and map be used or routinely modified to assess the ability of popperpicties of the invention of including antibodies and agoniss or amagenists of the invention of promote caspase protessis in paracratic apoptosis. Apoptosis in paracratic apoptosis. Apoptosis in paracratic apoptosis. Apoptosis in paracratic apoptosis. Apoptosis in marcatic apoptosis and assays for caspase apoptosis in an apoptosis and apoptosis and apoptosis and apoptosis of the invention of polypeptides of the invention including amplified and apoptosis of the invention including amplication and apoptosis of the invention including amplication and apoptosis of the invention including amplication and apost apoptosis and agoniss or an antipartic and (2)-235-34 (1996); 1293-54 (1996); 1294-140(2)-235-34 (1996); 1294-140(2)-235-34 (1996); 1294-140(2)-235-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)-236-34 (1996); 1294-140(2)- |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Regulation of epoptosis in pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 471                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HEDB47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <i>L</i> 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| 472 Activation of F.Cell p.58 or J.N. Signaling Pathway. | 1667)-1843 (2001), ricedo I, or discutes (as described in the 1699). Talks 19 (2001), ricedo I, or discutes (as described in the 1699). Talks 19 (2001), ricedo I, or discutes (as described in the 1699). Let et al., 19 (2009). Let | Kinase sasy, NK and p38 kinase perferred infocations include assys for signal transduction that regulare cell proliferation, activation, below mader "Hyporproliferative or apopusase are well known in the art. Disorders", blood disorders (e.g., sa and may be used or routinely modified to assess the ability of polypeptics of the invention Disorders", and/or "Blood-Related Including antipolics and agoniss or Disorders", and/or "Blood-Related Disor |
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|                                                          | 1. (1467) Add al., (1467) Add al., (1467) Add al., (1467) Add al., (1567) Add Add Add Add Add Add Add Add Add Ad                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | bū                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| under "Infectious Disease"). Highly<br>preferred indications include        | autominime diseases (e.g.,<br>rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis                                         | immunodeficiencies (e.g., as     | described below). Additional highly   | preferred indications include         | inflammation and inflammatory          | disorders. Highly preferred  | indications also include neoplastic | diseases (e.g., leukemia, lymphoma, | and/or as described below under | "Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as, | leukemia, lymphoma, prostate,      | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver, | and urinary cancer. Other preferred | indications include benign             | dysproliferative disorders and pre- | neoplastic conditions, such as, for           | example, hyperplasia, metaplasia,   | and/or dysplasia. Preferred        | indications include arthritis, asthma, | AIDS, allergy, anemia, pancytopenia, | leukopenia, thrombocytopenia, | Hodgkin"s disease, acute | lymphocytic anemia (ALL), | plasmacytomas, multiple myeloma, | Burkitt"s lymphoma, granulomatous | disease, inflammatory bowel disease, | sepsis, psoriasis, suppression of | immune reactions to transplanted | organs and tissues, endocarditis, |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|------------------------------|-------------------------------------|-------------------------------------|---------------------------------|----------------------------------|--------------------------------------|---------------------------------|------------------------------------|----------------------------------|------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|--------------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------------|-----------------------------------|--------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|
| promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and | JNK and p38 kinase activity that may                               | be used or routinely modified to test TNK and p38 kinged induced activity | of polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110 | (1998); Gupta et al., Exp Cell Res  | 247(2): 495-504 (1999); Kyriakis    | M, Biochem Soc Symp 64:29-48    | (1999); Chang and Karin, Nature  | 410(6824):37-40 (2001); and Cobb     | MH, Prog Biophys Mol Biol 71(3- | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its   | entirety. T cells that may be used  | according to these assays are publicly | available (e.g., through the        | ATCC <sup>TM</sup> ). Exemplary mouse T cells | that may be used according to these | assays include the CTLL cell line, | which is an IL-2 dependent             | suspension-culture cell line with    | cytotoxic activity.           |                          |                           |                                  |                                   |                                      |                                   |                                  |                                   |
|                                                                             |                                                                    |                                                                           |                                  |                                       |                                       |                                        |                              |                                     |                                     |                                 |                                  |                                      |                                 |                                    |                                  |                                    |                                     |                                        |                                     |                                               |                                     |                                    |                                        |                                      |                               |                          |                           |                                  |                                   |                                      |                                   |                                  |                                   |
|                                                                             |                                                                    |                                                                           |                                  |                                       |                                       |                                        |                              |                                     |                                     |                                 |                                  |                                      |                                 |                                    |                                  |                                    |                                     |                                        |                                     |                                               |                                     |                                    |                                        |                                      |                               |                          |                           |                                  |                                   |                                      |                                   |                                  |                                   |
|                                                                             |                                                                    |                                                                           |                                  |                                       |                                       |                                        |                              |                                     |                                     |                                 |                                  |                                      |                                 |                                    |                                  |                                    |                                     |                                        |                                     |                                               |                                     |                                    |                                        |                                      |                               |                          |                           |                                  |                                   |                                      |                                   |                                  |                                   |

| meningitis, and Lyme Disease. | A highly preferred indication is  | diabetes mellitus. An additional      | highly preferred indication is a     | complication associated with          | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and       | disorders as described in the      | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the      | "Endocrine Disorders" section       | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious  | _                                 | of the urinary tract and skin), carpal | tunnel evndrome and Dumistren's |
|-------------------------------|-----------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-------------------------------|-----------------------------------|----------------------------------------|---------------------------------|
|                               | Assays for measuring secretion of | insulin are well-known in the art and | may be used or routinely modified to | assess the ability of polypeptides of | the invention (including antibodies   | and agonists or antagonists of the   | invention) to stimulate insulin   | secretion. For example, insulin        | secretion is measured by FMAT      | using anti-rat insulin antibodies.   | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000); | Salapatek, A.M., et al., Mol       | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S ct. al.,    | Journal of Biomolecular Screening,  | 4:193-204 (1999), the contents of   | each of which is herein incorporated | by reference in its entirety. | Pancreatic cells that may be used | according to these assays are publicly | Ornitohio o through the ATCCTM  |
|                               | Insulin Secretion                 |                                       |                                      |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                   |                                        |                                 |
| _                             | 472                               |                                       |                                      |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                   |                                        |                                 |
|                               | HE2NV57                           |                                       |                                      |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                   |                                        |                                 |
|                               |                                   | 89                                    |                                      |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                   |                                        |                                 |

| contracture). An additional high preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss of alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | disheres mellins, an additional disheres mellins, an additional highly preferred indication is a mornication associated with disheres for the state of the state |
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| and/or may be routinely generated.  Remplar paractic cells that may be used according to these assays the used according to these assays and address of the property of the pr | aways for the regulation of violity and proliferation of cells in vitro are well-known in the art and may be used rountinely modified to assess the ability of polypeptides of the invention (including anthodizes and agonisis or attagonists of the travention (including anthodizes and agonisis or attagonists of the travention) to longulate viability and proliferation of pancreatic beta cells polylication of pancreatic beta cells. Incumple of cell fitter-clid librariessent cell viability assay in callure based on quantitation of the AIP present which signals the cells. Exemplary assays that many be cells. Exemplary assays that may be cells. Exemplary assays that may be regulation of viability and coruntariely modified to test regulation of viability and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Regulation of vinbility man prohibition of pancratic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 473                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | нг2РН3-6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>3</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| differen  | differentiation Examplem accore for    | embodiment of the instantion           |
|-----------|----------------------------------------|----------------------------------------|
| 19 7/03   | EDV binoce activity that may be used   | includes a mathod for inhihiting       |
| or routi  | or routinely modified to test FRK      | adinocyte differentiation A            |
| -i-seuix  | kinase-induced activity of             | highly preferred embodiment of the     |
| polypep   | polypeptides of the invention          | invention includes a method for        |
| (includi  | (including antibodies and agonists or  | stimulating (e.g., increasing)         |
| antagon   | antagonists of the invention) include  | adipocyte activation. An alternative   |
| the assa  | the assays disclosed in Forrer et al., | highly preferred embodiment of the     |
| Biol Ch   | Biol Chem 379(8-9):1101-1110           | invention includes a method for        |
| (1998);   | (1998); Le Marchand-Brustel Y, Exp     | inhibiting the activation of (e.g.,    |
| Clin En   | Clin Endocrinol Diabetes               | decreasing) and/or inactivating        |
| 107(2):   | 107(2):126-132 (1999); Kyriakis JM,    | adipocytes. Highly preferred           |
| Biocher   | Biochem Soc Symp 64:29-48 (1999);      | indications include endocrine          |
| Chang     | Chang and Karin, Nature                | disorders (e.g., as described below    |
| 410(682   | 410(6824):37-40 (2001); and Cobb       | under "Endocrine Disorders").          |
| MH, Pr    | MH, Prog Biophys Mol Biol 71(3-        | Highly preferred indications also      |
| 4):479-:  | 4):479-500 (1999); the contents of     | include neoplastic diseases (e.g.,     |
| each of   | each of which are herein               | lipomas, liposarcomas, and/or as       |
| incorpo   | incorporated by reference in its       | described below under                  |
| entirety  | entirety. Mouse adipocyte cells that   | "Hyperproliferative Disorders").       |
| may be    | may be used according to these         | Preferred indications include blood    |
| assays    | assays are publicly available (e.g.,   | disorders (e.g., hypertension,         |
| through   | through the ATCCTM). Exemplary         | congestive heart failure, blood vessel |
| nouse     | mouse adipocyte cells that may be      | blockage, heart disease, stroke,       |
| nsed ac   | used according to these assays         | impotence and/or as described below    |
| include   | include 3T3-L1 cells. 3T3-L1 is an     | under "Immune Activity",               |
| adheren   | adherent mouse preadipocyte cell       | "Cardiovascular Disorders", and/or     |
| line that | ine that is a continuous substrain of  | "Blood-Related Disorders"), immune     |
| 3T3 fib   | 3T3 fibroblast cells developed         | disorders (e.g., as described below    |
| through   | through clonal isolation and undergo   | under "Immune Activity"), neural       |
| a pre-ad  | a pre-adipocyte to adipose-like        | disorders (e.g., as described below    |
| convers   | conversion under appropriate           | under "Neural Activity and             |
| differen  | differentiation conditions known in    | Neurological Diseases"), and           |
| the art.  |                                        | infection (e.g., as described below    |
|           |                                        | under "Infectious Disease").           |
|           |                                        | indi                                   |
|           |                                        | diabetes mellitus. An additional       |

|         |     |                                                                 |                                                                                                                   | weight loss or alternatively, weight gain. Additional highly greenered indications are alterned indications are alterned indications are disordered indications are disordered of the perved indications are disordered of the musculoskeletal systems of the musculoskeletal systems the musculoskeletal systems of the musculoskeletal systems of the pervent and the pervention in include, systems of the pervention in include, and the pervention in include, systems of the pervention in include and pervention in include and pervention in include and form of the pervention in include and formy disease, of disorders, earlier disorders, flitnosis, cauberia, and debrow disease or disorders. Perferred indications include melanoma, prostate, lung, melanoma, prostate, lung, metal and trainey cancer. Additional melanoma, prostate, lung, mercanter, espolisageal, stommed, brani, liver, and urinany cancer. |
|---------|-----|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |     |                                                                 |                                                                                                                   | Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign disconting disconting and was                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         |     |                                                                 |                                                                                                                   | uysponiteanye unsutetis anu pre-<br>ncoplastic conditions, such as, for<br>example, hyperplasia, metaplasia,<br>and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| HE8DS15 | 474 | Regulation of<br>transcription of Malic<br>Enzyme in adipocytes | Assays for the regulation of<br>transcription of Malic Enzyme are<br>well-known in the art and may be             | A highly preferred indication is<br>diabetes mellitus. An<br>additional highly preferred indication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|         |     | •                                                               | used or routinely modified to assess<br>the ability of polypeptides of the<br>invention (including antibodies and | is a complication associated with<br>diabetes (e.g., diabetic retinopathy,<br>diabetic nephropathy, kidney disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| agonists or antagonists of the               | (e o renal failure nenhronathy          |
|----------------------------------------------|-----------------------------------------|
| for morting to require tension of            |                                         |
| Malic Enzyme, a key enzyme in                |                                         |
| lipogenesis. Malic enzyme is                 | section below), diabetic neuropathy,    |
| involved in lipogenesisand its               | nerve disease and nerve damage          |
| expression is stimulted by insulin.          | (e.g., due to diabetic neuropathy),     |
| ME promoter contains two direct              | blood vessel blockage, heart disease,   |
| repeat (DR1)- like elements MEp              | _                                       |
| and MEd identified as putative PPAR          | R   diabetic neuropathy or blood vessel |
| response elements. ME promoter               | blockage), seizures, mental             |
| may also responds to AP1 and other           | confusion, drowsiness, nonketotic       |
| transcription factors. Exemplary             | hyperglycemic-hyperosmolar coma,        |
| assays that may be used or routinely         | cardiovascular disease (e.g., heart     |
| modified to test for regulation of           | disease, atherosclerosis,               |
| transcription of Malic Enzyme (in            | microvascular disease, hypertension,    |
| adipoocytes) by polypeptides of the          | stroke, and other diseases and          |
| invention (including antibodies and          | disorders as described in the           |
| agonists or antagonists of the               | "Cardiovascular Disorders" section      |
| invention) include assays disclosed          | below), dyslipidemia, endocrine         |
| in: Streeper, R.S., et al., Mol              | Ť                                       |
| Endocrinol, 12(11):1778-91 (1998);           | -                                       |
| Garcia-Jimenez, C., et al., Mol              | below), neuropathy, vision              |
| Endocrinol, 8(10):1361-9 (1994);             | impairment (e.g., diabetic retinopathy  |
| Barroso, I., et al., J Biol Chem,            | and blindness), ulcers and impaired     |
| 274(25):17997-8004 (1999);                   | wound healing, and infection (e.g.,     |
| ljpenberg, A., et al., J Biol Chem,          | infectious diseases and disorders as    |
| 272(32):20108-20117 (1997);                  | described in the "Infectious            |
| Berger, et al., Gene 66:1-10 (1988);         | Diseases" section below, especially     |
| and, Cullen, B., et al., Methods in          | of the urinary tract and skin), carpal  |
| Enzymol. 216:362–368 (1992), the             | tunnel syndrome and Dupuytren's         |
| contents of each of which is herein          | contracture). An additional             |
| incorporated by reference in its             | highly preferred indication is obesity  |
| entirety. Hepatocytes that may be            | and/or complications associated with    |
| used according to these assays are           | obesity. Additional highly preferred    |
| publicly available (e.g., through the        | indications include weight loss or      |
| ATCC <sup>TM</sup> ) and/or may be routinely | alternatively, weight gain.             |
| generated. Exemplary hepatocytes             | Aditional highly preferred              |

| indications are complications associated with insulin resistance.                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | immunological and inflash preferred inflash preferred inflammancy discussing a confidence (e.g., solid series). The series active and a series and the series of the series in the series of the series in the serie |
|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| that may be used according to these assays includes the H4IIE rat liver hepatoma cell line. | regulatory and octing exquence of<br>perpetred Assay. construct contains<br>regulatory and octing exquence of<br>sugarders synthesize, the first specific<br>cozyme in the cholestend<br>sugarders of the content of<br>al., 13 ind. Chem. 26s12818,<br>128241(993), the contents of which<br>we therein incorporated by reference<br>in its entirety. Cells were treated<br>with SID supermeants, and State.<br>In 18 continey, Cells were treated<br>in its entirety. Cells were treated<br>activity was measured after 72 hours.<br>HeCQL is in human bepancediblate<br>earchinoma cell line (ATCO' HB).<br>2006-55, Sec Knowles et al., Science.<br>2006-497-9 (1980), the contents of<br>which are before incorporated by<br>reference in its entirety. | are well known in the art and may be a<br>wear well known in the art and may be a<br>and or rounishey modified to assess the shilty of polyperpides of the inversion (including anthodies and agonists or antaquies of the inversion (including anthodies and agonists or antaquies of the inversion) to regulate production and securities of III. As for example, FMAT may be used or wearing the and the application of the ability of polyperpides of the ability of polyperpides of the agonists or antagonists of the autention) to regulate production and/or secretion of II8 from and or secretion of II8 from and or secretion of II8 from and or secretion of II8 from manifical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion of II8 from multilical very necessary and a secretion o                                                   |
|                                                                                             | synthetics of squalenc<br>synthetics gree<br>franstription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Absolution of IL-8 by production of IL-8 by production cults of the strength o |
|                                                                                             | 474                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 475                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                             | HEBDS115                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HE9CO69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                             | 70                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| deductes (e.g. such as described below under "Cations scribed below under "Cations scribed below under "Cations scribed from the properties of the complications (such from the morphism of the seattine respiratory distress syndrome and sepsia such sie share respiratory distress syndrome and sepsiatory distress syndrome and resulting from septic shock, restanosis and atherosclerosis.                                                                           | A highly preferred emboliment of the invention includes a method for simulating appropria profileration. An alternative highly preferred emboliment of the invention includes a method for simulating adjacype differentiation. A highly preferred emboliment of the modeliment of the invention includes a method for inhibiting and procyce differentiation. A highly preferred emboliment of the simulating (e.g., increasing) succession and alternative flightly preferred emboliment of the inhibiting the activation of (e.g., increasing) invention includes a method for inhibiting the activation of (e.g., intrecining includes a method for inhibiting the activation of (e.g., intelliting the activation of (e.g., inhibiting the activation of (e.g., inhibiting the activation of individuing adioxyces. Highly preferred emboliment of the inhibiting the activation of enderence inhibiting the activation of individuing                |
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| UNIVEC). HUVE/Cs are<br>cendonleil cells which line verous<br>blood vessels, and are involved in<br>limitorios flat include, but are not<br>limited to, anglogenesis, vascular<br>membellity, vascular tone, and<br>immune cell extravastion.<br>And control and pay a pivolal role<br>in the infation and perpetuation of<br>in the infation and severeion of IL-8<br>may play an important role in<br>rectalinates and serveion of immune<br>cell sards as transpolitis, | the countyle and Elle/ Itimase assays, for example an Elle/ Itimase assays, for the coll polification of alle/ Itimase assays, for the coll polification of differentiation end prolification of differentiation are well known in the art and may be used or routinely modified to assess the ability of forgogreptics of the invention (including authorities and argonists or anagonists or anagonists of the invention) to promuse or inhit tell invention) and the far kinnes activity that may be used the far wention (uncluding authorities and agoniss or authority of the invention) include the assays disclosed in Forter et al., and Chen 3799 (20):1101-1110 (1998), Le Marchand-Brande Y. Fixth [1998], Le Marchand-Brande Y. Fixth [1998], Le Marchand-Brande Y. Fixth [1999], Krinkis JM, (1998), Le Marchand-Brande Y. Fixth [1997], Fixthakis JM, [1998], Le Marchand-Brande Y. Fixthakis JM, [1997], Fixthakis JM, |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Adrivation of Agraviton of Signaling Pathway Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 476                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HEHNOT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| Biochem Soc Symp 64:29-48 (1999):      | indications include endocrine          |
|----------------------------------------|----------------------------------------|
| Chang and Karin Nature                 |                                        |
| 410(6824);37-40 (2001); and Cobb       | under "Endocrine Disorders").          |
| MH, Prog Biophys Mol Biol 71(3-        | Highly preferred indications also      |
| 4):479-500 (1999); the contents of     | include neoplastic diseases (e.g.,     |
| each of which are herein               | lipomas, liposarcomas, and/or as       |
| incorporated by reference in its       | described below under                  |
| entirety. Mouse adipocyte cells that   | "Hyperproliferative Disorders").       |
| may be used according to these         | Preferred indications include blood    |
| assays are publicly available (e.g.,   | disorders (e.g., hypertension,         |
| through the ATCCTM). Exemplary         | congestive heart failure, blood vessel |
| mouse adipocyte cells that may be      | blockage, heart disease, stroke,       |
| used according to these assays         | impotence and/or as described below    |
| include 3T3-L1 cells. 3T3-L1 is an     | under "Immune Activity",               |
| adherent mouse preadipocyte cell       | "Cardiovascular Disorders", and/or     |
| line that is a continuous substrain of | "Blood-Related Disorders"), immune     |
| 3T3 fibroblast cells developed         | disorders (e.g., as described below    |
| through clonal isolation and undergo   | under "Immune Activity"), neural       |
| a pre-adipocyte to adipose-like        | disorders (e.g., as described below    |
| conversion under appropriate           | under "Neural Activity and             |
| differentiation conditions known in    | Neurological Diseases"), and           |
| the art.                               | infection (e.g., as described below    |
|                                        | under "Infectious Disease").           |
|                                        | A highly preferred indication is       |
|                                        | diabetes mellitus. An additional       |
|                                        | highly preferred indication is a       |
|                                        | complication associated with           |
|                                        | diabetes (e.g., diabetic retinopathy,  |
|                                        | diabetic nephropathy, kidney disease   |
|                                        | (e.g., renal failure, nephropathy      |
|                                        | and/or other diseases and disorders as |
|                                        | described in the "Renal Disorders"     |
|                                        | section below), diabetic neuropathy,   |
|                                        | nerve disease and nerve damage         |
|                                        | (e.g., due to diabetic neuropathy),    |
|                                        | blood vessel blockage, heart disease,  |
|                                        | stroke, impotence (e.g., due to        |

|  | diabetic neuropathy or blood vessel<br>blockage), seizures, mental      |
|--|-------------------------------------------------------------------------|
|  | confusion, drowsiness, nonketotic                                       |
|  | hyperglycemic-hyperosmolar coma,<br>cardiovascular disease (e.g., heart |
|  | disease, atherosclerosis,                                               |
|  | microvascular disease, hypertension,                                    |
|  | disorders as described in the                                           |
|  | "Cardiovascular Disorders" section                                      |
|  | below), dyslipidemia, endocrine                                         |
|  | disorders (as described in the                                          |
|  | below), neuropathy, vision                                              |
|  | impairment (e.g., diabetic retinopathy                                  |
|  | and blindness), ulcers and impaired                                     |
|  | wound healing, infection (e.g.,                                         |
|  | infectious diseases and disorders as                                    |
|  | described in the "Infectious                                            |
|  | Discases" section below (particularly                                   |
|  | of the urinary tract and skin). An                                      |
|  | additional highly preferred indication                                  |
|  | is obesity and/or complications                                         |
|  | associated with obesity. Additional                                     |
|  | highly preferred indications include                                    |
|  | 9                                                                       |
|  | gain. Additional highly                                                 |
|  | preferred indications are                                               |
|  | us ass                                                                  |
|  | resistance. Additional highly                                           |
|  | preferred indications are disorders of                                  |
|  | the musculoskeletal systems                                             |
|  | including myopathies, muscular                                          |
|  | dystrophy, and/or as described                                          |
|  | herein. Additional highly                                               |
|  | preferred indications include,                                          |
|  | hypertension, coronary artery                                           |

| disease, dysitioning gallsones, ostoonthisis, degenerative arthritis, exponentinis, degenerative arthritis, and kidney diseases or disorders.  Perferrate disorders include and kidney diseases or disorders, proprietors include proplement and texact; such as proplement and texact; such as proplement and texact; such as proprietory disclarations include medianoma, possessed, lung, participated inficialities include himmon, liver, and unimary cancer. Highly preferred indications include himmons and prosucomate. Other preferred indications include being the dysportificative disorders and prenoplastic conditions, such as, for example, hyperplastia, metaplastia, meta | Assays for the regulation of the production of the regulation of t |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Explaint on of transacrition through the FAS promoter element in hepatocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 476                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | H9HY07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 27                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| Ę                                                                                                     |                                                                         | Ē                                  |                                        |                                       |                                   | athy                                  | pg                                    |                                      | as                                   |                                 | ly.                                   | al                                     |                                       |                                      | sity                                   | vith                                 | ped                                  |                                   |                                |                                         |                                 |                                     |                                  | as                                    | 9                                     |                                       |                                      |                                      | peq                                     |                                     | , as                                   | 7                                     |
|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------|----------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|---------------------------------|---------------------------------------|----------------------------------------|---------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|-----------------------------------------|---------------------------------|-------------------------------------|----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------------|-------------------------------------|----------------------------------------|---------------------------------------|
| cardiovascular disease (e.g., heart<br>disease, atherosclerosis,                                      | stroke, and other diseases and<br>disorders as described in the         | 'Cardiovascular Disorders" section | below), dyslipidemia, endocrine        | disorders (as described in the        | clow), neuropathy, vision         | mpairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired   | wound healing, and infection (e.g.,  | infectious diseases and disorders as | described in the "Infectious    | Diseases" section below, especially   | of the urinary tract and skin), carpal | unnel syndrome and Dupuytren's        | An additional                        | nighly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | ndications include weight loss or | weight gain.                   | nly preferred                           | ndications are complications    | associated with insulin resistance. | Highly preferred indications     | include endocrine disorders (e.g., as | described below under "Endocrine      | Disorders") and disorders of the      | tal system.                          | Preferred indications include        | neoplastic diseases (e.g., as described | below under "Hyperproliferative     | Disorders"), blood disorders (e.g., as | described below under "Immune         |
| cardiovascular disease ( disease, atherosclerosis                                                     | stroke, and of                                                          | "Cardiovascul                      | below), dyslig                         | disorders (as c                       | below), neuro                     | impairment (e                         | and blindness                         | wound healing                        | infectious disc                      | described in the                | Diseases" seci                        | of the urinary                         | tunnel syndro                         | contracture).                        | highly preferr                         | and/or compli                        | obesity. Addi                        | indications in                    | alternatively, weight gain     | Aditional highly preferred              | indications are                 | associated wit                      | Highly pre                       | include endoc                         | described belo                        | Disorders") ar                        | musculoskeletal system.              | Preferred indi                       | neoplastic dis                          | below under "                       | Disorders"), b                         | described belo                        |
| Exemplary assays that may be used or routinely modified to test for FAS monotone element activity (in | hepatocytes) by polypeptides of the invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed in | Xiong, S., et al., Proc Natl Acad Sci | Roder, K., et al., Eur J Biochem, | 260(3):743-51 (1999); Oskouian B,     | et al., Biochem J, 317 ( Pt 1):257-65 | (1996); Berger, et al., Gene 66:1-10 | (1988); and, Cullen, B., et al.,     | Methods in Enzymol. 216:362-368 | (1992), the contents of each of which | is herein incorporated by reference in | its entirety. Hepatocytes that may be | used according to these assays, such | as H4IIE cells, are publicly available | (e.g., through the ATCCTM) and/or    | may be routinely generated.          | Exemplary hepatocytes that may be | used according to these assays | include rat liver hepatoma cell line(s) | inducible with glucocorticoids, | insulin, or cAMP derivatives.       | Kinase assay. Kinase assays, for | examplek Elk-1 kinase assays, for     | ERK signal transduction that regulate | cell proliferation or differentiation | are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the      | invention (including antibodies and | agonists or antagonists of the         | invention) to promote or inhibit cell |
|                                                                                                       |                                                                         |                                    |                                        |                                       |                                   |                                       |                                       |                                      |                                      |                                 |                                       |                                        |                                       |                                      |                                        |                                      |                                      |                                   |                                |                                         |                                 |                                     | Activation of Skeletal           | Muscle Cell ERK                       | Signalling Pathway                    |                                       |                                      |                                      |                                         |                                     |                                        |                                       |
|                                                                                                       |                                                                         |                                    |                                        |                                       |                                   |                                       |                                       |                                      |                                      |                                 |                                       |                                        |                                       |                                      |                                        |                                      |                                      |                                   |                                |                                         |                                 |                                     | 477                              |                                       |                                       |                                       |                                      |                                      |                                         |                                     |                                        |                                       |
|                                                                                                       |                                                                         |                                    |                                        |                                       |                                   |                                       |                                       |                                      |                                      |                                 |                                       |                                        |                                       |                                      |                                        |                                      |                                      |                                   |                                |                                         |                                 |                                     | HE90W20                          |                                       |                                       |                                       |                                      |                                      |                                         |                                     |                                        |                                       |
|                                                                                                       |                                                                         |                                    |                                        |                                       |                                   |                                       |                                       |                                      |                                      |                                 |                                       |                                        |                                       |                                      |                                        |                                      |                                      |                                   |                                |                                         |                                 |                                     |                                  | 73                                    |                                       |                                       |                                      |                                      |                                         |                                     |                                        |                                       |

|                                | 7                                 | ьi                                   | 9                                | as                                     |                               |                                       |                                       |                                        |                               |                                    |                                |                                     |                                   |                                |                                    |                                   |                                    | _                                  | ıy,                                  |                                       |                                     | s,                                    |                                              | ы<br>П                              |                                      |                                     | la,                                   |                                     |                           | ou,                                     |                                |                               |                                    |                                 |                                |                               |
|--------------------------------|-----------------------------------|--------------------------------------|----------------------------------|----------------------------------------|-------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|-------------------------------|------------------------------------|--------------------------------|-------------------------------------|-----------------------------------|--------------------------------|------------------------------------|-----------------------------------|------------------------------------|------------------------------------|--------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|---------------------------|-----------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|
| Activity", "Cardiovascular     | Disorders", and/or "Blood-Related | Disorders"), immune disorders (e.g., | as described below under "Immune | Activity"), neural disorders (e.g., as | described below under "Neural | Activity and Neurological             | Diseases"), and infection (e.g., as   | described below under "Infectious      | Disease"). A highly preferred | indication is diabetes mellitus.   | An additional highly preferred | indication is a complication        | associated with diabetes (e.g.,   | diabetic retinopathy, diabetic | nephropathy, kidney disease (e.g., | renal failure, nephropathy and/or | other diseases and disorders as    | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage        | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to              | diabetic neuropathy or blood vessel | blockage), seizures, mental          | confusion, drowsiness, nonketotic   | hyperglycemic-hyperosmolar coma,      | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension,    | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section |
| proliferation, activation, and | ssavs for                         | _                                    | st ERK                           | kinase-induced activity of             | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110  | (1998); Le Marchand-Brustel Y, Exp | Clin Endocrinol Diabetes       | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature        | 410(6824):37-40 (2001); and Cobb   | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein           | incorporated by reference in its     | entirety. Rat myoblast cells that may | 9                                   | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary rat myoblast | cells that may be used according to | these assays include L6 cells. L6 is | an adherent rat myoblast cell line, | isolated from primary cultures of rat | thigh muscle, that fuses to form    | 73                        | fibers after culture in differentiation | media.                         |                               |                                    |                                 |                                |                               |
|                                |                                   |                                      |                                  |                                        |                               |                                       |                                       |                                        |                               |                                    |                                |                                     |                                   |                                |                                    |                                   |                                    |                                    |                                      |                                       |                                     |                                       |                                              |                                     |                                      |                                     |                                       |                                     |                           |                                         |                                |                               |                                    |                                 |                                |                               |
|                                |                                   |                                      |                                  |                                        |                               |                                       |                                       |                                        |                               |                                    |                                |                                     |                                   |                                |                                    |                                   |                                    |                                    |                                      |                                       |                                     |                                       |                                              |                                     |                                      |                                     |                                       |                                     |                           |                                         |                                |                               |                                    |                                 |                                |                               |
|                                |                                   |                                      |                                  |                                        |                               |                                       |                                       |                                        |                               |                                    |                                |                                     |                                   |                                |                                    |                                   |                                    |                                    |                                      |                                       |                                     |                                       |                                              |                                     |                                      |                                     |                                       |                                     |                           |                                         |                                |                               |                                    |                                 |                                | _                             |

|  | helow) neuronathy vision               |
|--|----------------------------------------|
|  | impairment (e.g. dishetic retinonathy  |
|  | and blindness), ulcers and impaired    |
|  | wound healing, infection (e.g.,        |
|  | infectious diseases and disorders as   |
|  | <br>described in the "Infectious       |
|  | Diseases" section below, especially    |
|  | of the urinary tract and skin), carpal |
|  | tunnel syndrome and Dupuytren's        |
|  | contracture). An additional            |
|  | highly preferred indication is obesity |
|  | and/or complications associated with   |
|  | obesity. Additional highly preferred   |
|  | indications include weight loss or     |
|  | alternatively, weight gain.            |
|  | Aditional highly preferred             |
|  | indications are complications          |
|  | associated with insulin resistance.    |
|  | <br>Additional highly preferred        |
|  | indications are disorders of the       |
|  | musculoskeletal systems including      |
|  | myopathies, muscular dystrophy,        |
|  | and/or as described herein.            |
|  | <br>Additional highly preferred        |
|  | indications include: myopathy,         |
|  | atrophy, congestive heart failure,     |
|  | cachexia, myxomas, fibromas,           |
|  | congenital cardiovascular              |
|  | abnormalities, heart disease, cardiac  |
|  | arrest, heart valve disease, and       |
|  | vascular disease. Highly               |
|  | preferred indications include          |
|  | neoplasms and cancer, such as,         |
|  | rhabdomyoma, rhabdosarcoma,            |
|  | stomach, esophageal, prostate, and     |
|  | urinary cancer. Highly preferred       |
|  | indications also include breast, lung, |

|    |         |     |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | colon, pancreatic, brain, and liver<br>cancer. Other preferred indications<br>include benign dysproliferative<br>disorders and pre-neoplastic<br>conditions, such as, hyperplasia,<br>metaplasia, and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----|---------|-----|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 74 | HEEAG23 | 478 | Adiposite fill Adiposite fill X Signaling Pulthway | The company of the co | A highly preferred chmodiment of the invention includes a method for invention includes a method profileration. An alternative highly preferred embodiment of the inhibiting addrocyte proliferation. A highly preferred embodiment of the invention includes a method for inhibiting addrocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for any and alternative highly preferred embodiment of the invention includes a method for inhibiting any approved afferentiation. An alternative highly preferred embodiment of the invention includes a method for simulating (e.g., increasing) simulating (e.g., increasing) inhibiting the activation of (e.g., inhibiting the activation of experience of addrocrassing and or intercivating addrocytes. Highly preferred indications to she inhibiting the activation of the inhibiting the activation o |

| _ | P        | disorders as described in the           |
|---|----------|-----------------------------------------|
|   | <u> </u> | "Cardiovascular Disorders" section      |
|   | 9        | below), dyslipidemia, endocrine         |
|   | P        | disorders (as described in the          |
|   | <u>*</u> | "Endocrine Disorders" section           |
|   | 4        | below), neuropathy, vision              |
|   | ū        | impairment (e.g., diabetic retinopathy  |
|   | ed       | and blindness), ulcers and impaired     |
|   | *        | wound healing, infection (e.g.,         |
|   | · II     | infectious diseases and disorders as    |
|   | 70       | described in the "Infectious            |
|   | 1        | Diseases" section below (particularly   |
|   | 0        | of the urinary tract and skin). An      |
|   | -        | additional highly preferred indication  |
|   | -21      | is obesity and/or complications         |
|   | es       | associated with obesity. Additional     |
|   | ц        | highly preferred indications include    |
|   | #        | weight loss or alternatively, weight    |
|   | 500      | gain. Additional highly                 |
|   | £,       | preferred indications are               |
|   | <u> </u> | ons ass                                 |
|   | n n      | resistance. Additional highly           |
|   | £,       | preferred indications are disorders of  |
|   | - t      | the musculoskeletal systems             |
|   | ·i       | including myopathies, muscular          |
|   | p        | dystrophy, and/or as described          |
|   | п        | herein. Additional highly               |
|   | <u>6</u> | preferred indications include,          |
|   | n h      | hypertension, coronary artery           |
|   | p        | disease, dyslipidemia, gallstones,      |
|   | 0        | osteoarthritis, degenerative arthritis, |
|   | <u> </u> | eating disorders, fibrosis, cachexia,   |
|   | ed       | and kidney diseases or disorders.       |
|   | d        | Preferred indications include           |
|   | п        | neoplasms and cancer, such as,          |
|   |          | lymphoma, leukemia and breast,          |
|   |          | notion and bidness concer Additional    |

| preferred indications include nelements, prostate, hinge penceratic, coaptingeal, stometh, brain, liver, and urinary cancer. Highly preferred indications include hippones and ilyosurcoursa. Otter preferred indications include beings conditions, soft with each complexity conditions, soft as, for example, hypothistis, metaplists, and/or ophysits; metaplists, | Kinase saws, Kinase sawsy, for the invention includes a method for example an GSK-3 kinase assay, for the invention includes a method for example and extending and modified to sease the ability of modified to seases the ability of modified to sease the ability of modified to sease the ability of modified to sea PIS kinese conditioned, seldent muscle equal positioned in clinicals an enthod for thinking activity of polypopuloses of the modified to set PIS kinese, induced and Schreide a |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Addition of Skeelem (Rimes assay, Kinnes assays, for example an GSK-3 kinnes assay, for example an GSK-3 kinnes assay, for example an GSK-3 kinnes assay, for the control of the invention in challing antibodies and agontise to managonists of the invention in challing antibodies and agontise to promote or inhibit guizose.  Examplary assays for P13 kinnes and agontise or interduolism and cell survival.  Examplary assays for P13 kinnes challing antibodies and agontise or orining the control of the invention of including antibodies and general control of the invention of including antibodies and general control of the invention of including antibodies and pagentists or antigotises of the invention of including antibodies and agontise or antigotises of the invention of including antibodies and selected former et al., Dabetees 44(2):265-21 (2000), the countrol in incompanied by treferrors in its incompanied by treferrors in its control of the c |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HBEA(Q23 478 478 478 478 478 478 478 478 478 478                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | H                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| H                                     | muscie cen dinerentation. In a        |                                      |                                     | _                                    |                                     | _                                     | described below under            | _                                    | endocrine disorders (e.g., as           | described below under "Endocrine | Disorders"), neural disorders (e.g., as | described below under "Neural | Activity and Neurological | Diseases"), blood disorders (e.g., as | described below under "Immune | Activity", "Cardiovascular | Disorders", and/or "Blood-Related | Disorders"), immune disorders (e.g., | as described below under "Immune | Activity"), and infection (e.g., as | described below under "Infectious | Disease"). A highly preferred | indication is diabetes mellitus. | An additional highly preferred | indication is a complication | associated with diabetes (e.g., | diabetic retinopathy, diabetic | nephropathy, kidney disease (e.g., | renal failure, nephropathy and/or | other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage (e.g., | due to diabetic neuropathy), blood | vessel blockage, heart disease. |
|---------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------|--------------------------------------|-----------------------------------------|----------------------------------|-----------------------------------------|-------------------------------|---------------------------|---------------------------------------|-------------------------------|----------------------------|-----------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-----------------------------------|-------------------------------|----------------------------------|--------------------------------|------------------------------|---------------------------------|--------------------------------|------------------------------------|-----------------------------------|---------------------------------|------------------------------------|--------------------------------------|---------------------------------------|------------------------------------|---------------------------------|
| entirety. Rat myoblast cells that may | be used according to these assays are | ATCCTM) Events and any rat modellast | cells that may be used according to | these assays include L6 cells. L6 is | an adherent rat myoblast cell line, | isolated from primary cultures of rat | thigh muscle, that fuses to form | multinucleated myotubes and striated | fibers after culture in differentiation | media.                           |                                         |                               |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |                               |                                  |                                |                              |                                 |                                |                                    |                                   |                                 |                                    |                                      |                                       |                                    |                                 |
|                                       |                                       |                                      |                                     |                                      |                                     |                                       |                                  |                                      |                                         |                                  |                                         |                               |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |                               |                                  |                                |                              |                                 |                                |                                    |                                   |                                 |                                    |                                      |                                       |                                    |                                 |
|                                       |                                       |                                      |                                     |                                      |                                     |                                       |                                  |                                      |                                         |                                  |                                         |                               |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |                               |                                  |                                |                              |                                 |                                |                                    |                                   |                                 |                                    |                                      |                                       |                                    | _                               |

|  | stroke, impotence (e.g., due to        |
|--|----------------------------------------|
|  | diabetic neuropathy or blood vessel    |
|  | blockage), seizures, mental            |
|  | confusion, drowsiness, nonketotic      |
|  | hyperglycemic-hyperosmolar coma,       |
|  | cardiovascular disease (e.g., heart    |
|  | disease, atherosclerosis,              |
|  | microvascular disease, hypertension,   |
|  | stroke, and other diseases and         |
|  | disorders as described in the          |
|  | "Cardiovascular Disorders" section     |
|  | below), dyslipidemia, endocrine        |
|  | disorders (as described in the         |
|  | "Endocrine Disorders" section          |
|  | below), neuropathy, vision             |
|  | impairment (e.g., diabetic retinopathy |
|  | and blindness), ulcers and impaired    |
|  | wound healing, infections (e.g.,       |
|  | infectious diseases and disorders as   |
|  | described in the "Infectious           |
|  | Diseases" section below, especially    |
|  | of the urinary tract and skin), carpal |
|  | tunnel syndrome and Dupuytren's        |
|  | contracture). An additional            |
|  | highly preferred indication is obesity |
|  | and/or complications associated with   |
|  | obesity. Additional highly preferred   |
|  | indications include weight loss or     |
|  | alternatively, weight gain.            |
|  | Additional highly preferred            |
|  | indications are complications          |
|  | associated with insulin resistance.    |
|  | Additional highly preferred            |
|  | indications are disorders of the       |
|  | musculoskeletal system including       |
|  | myopathies, muscular dystrophy,        |
|  | and/or as described herein.            |

| Additional highly preferred includes also good and account of the | An highly peterned indication is diabetes mellitus. The additional lightly perferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic retinopathy, diabetic retinopathy, diabetic retinopathy, diabetic retinopathy, in the complex of th |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Assays for measuring secretion of insulin are well-known in the art and may be used or northeigh modified to assess the shilty of polygodies of the invention flowthing antibodies and agonists or antagonists of the invention po stimulate risalin securetion. For example, Insulin securetion for summittee risalin securetion is neusanted by PMAY insulin securetion from patternated by the partial insulin securetion from patternate obea of its inpregiated by glucose and also by octam proteins/petides, and also by octam proteins/petides, and diabetes. Exemptiny assisys that may diabetes. Exemptiny modified to test                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | secretion from paracretic bear cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 479                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | IHOMQ63                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 27                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                   | (from pancreatic cells) by              | hyperglycemic-hyperosmolar coma.       |
|----|---------|-----|-------------------|-----------------------------------------|----------------------------------------|
|    |         |     |                   | polypeptides of the invention           | cardiovascular disease (e.g., heart    |
|    |         |     |                   | (including antibodies and agonists or   | discase, atherosclerosis,              |
|    |         |     |                   | antagonists of the invention) include   | microvascular disease, hypertension,   |
|    |         |     |                   | assays disclosed in: Ahren, B., et al., | stroke, and other diseases and         |
|    |         |     |                   | Am J Physiol, 277(4 Pt 2):R959-66       | disorders as described in the          |
|    |         |     |                   | (1999); Li, M., et al., Endocrinology,  | "Cardiovascular Disorders" section     |
|    |         |     |                   | 138(9):3735-40 (1997); Kim, K.H.,       | below), dyslipidemia, endocrine        |
|    |         |     |                   | et al., FEBS Lett, 377(2):237-9         | disorders (as described in the         |
|    |         |     |                   | (1995); and, Miraglia S ct. al.,        | "Endocrine Disorders" section          |
|    |         |     |                   | Journal of Biomolecular Screening,      | below), neuropathy, vision             |
|    |         |     |                   | 4:193-204 (1999), the contents of       | impairment (e.g., diabetic retinopathy |
|    |         |     |                   | each of which is herein incorporated    | and blindness), ulcers and impaired    |
|    |         |     |                   | by reference in its entirety.           | wound healing, and infection (e.g.,    |
|    |         |     |                   | Pancreatic cells that may be used       | infectious diseases and disorders as   |
|    |         |     |                   | according to these assays are publicly  | described in the "Infectious           |
|    |         |     |                   | available (e.g., through the ATCCTM)    | Discases" section below, especially    |
|    |         |     |                   | and/or may be routinely generated.      | of the urinary tract and skin), carpal |
|    |         |     |                   | Exemplary pancreatic cells that may     | tunnel syndrome and Dupuytren's        |
|    |         |     |                   | be used according to these assays       | contracture). An additional            |
|    |         |     |                   | include rat INS-1 cells. INS-1 cells    | highly preferred indication is obesity |
|    |         |     |                   | are a semi-adherent cell line           | and/or complications associated with   |
|    |         |     |                   | established from cells isolated from    | obesity. Additional highly preferred   |
|    |         |     |                   | an X-ray induced rat transplantable     | indications include weight loss or     |
|    |         |     |                   | insulinoma. These cells retain          | alternatively, weight gain.            |
|    |         |     |                   | characteristics typical of native       | Aditional highly preferred             |
|    |         |     |                   | pancreatic beta cells including         | indications are complications          |
|    |         |     |                   | glucose inducible insulin secretion.    | associated with insulin resistance.    |
|    |         |     |                   | References: Asfari et al.               |                                        |
|    |         |     |                   | Endocrinology 1992 130:167.             |                                        |
|    | HEPAB80 | 480 | Activation of     | Kinase assay. Kinase assays, for        | A highly preferred embodiment          |
| 9/ |         |     | Adipocyte ERK     | example an Elk-1 kinase assay, for      | of the invention includes a method     |
|    |         |     | Signaling Pathway | ERK signal transduction that regulate   | for stimulating adipocyte              |
|    |         |     |                   | cell proliferation or differentiation   | proliferation. An alternative highly   |
|    |         |     |                   | are well known in the art and may be    | preferred embodiment of the            |
|    |         |     |                   | used or routinely modified to assess    | invention includes a method for        |
|    |         |     |                   | the ability of polypeptides of the      | inhibiting adipocyte proliferation.    |

| A highly preferred embodiment of    | the invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention           | includes a method for inhibiting     | adipocyte differentiation. A      | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        |
|-------------------------------------|-------------------------------------|----------------------------------------|---------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|
| invention (including antibodies and | agonists or antagonists of the      | invention) to promote or inhibit cell  | proliferation, activation, and  | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodics and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in |
|                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |
|                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |

|  | the art | infaction (a g as described helour     |
|--|---------|----------------------------------------|
|  | The art | micental (c.g., as described octon     |
|  |         | under infectious Disease ).            |
|  |         | ğ                                      |
|  |         | diabetes mellitus. An additional       |
|  |         | highly preferred indication is a       |
|  |         | complication associated with           |
|  |         | diabetes (e.g., diabetic retinopathy,  |
|  |         | diabetic nephropathy, kidney disease   |
|  |         | (e.g., renal failure, nephropathy      |
|  |         | and/or other diseases and disorders as |
|  |         | described in the "Renal Disorders"     |
|  |         | section below), diabetic neuropathy,   |
|  |         | nerve disease and nerve damage         |
|  |         | (e.g., due to diabetic neuropathy),    |
|  |         | blood vessel blockage, heart disease,  |
|  |         | stroke, impotence (e.g., due to        |
|  |         | diabetic neuropathy or blood vessel    |
|  |         | blockage), seizures, mental            |
|  |         | confusion, drowsiness, nonketotic      |
|  |         | hyperglycemic-hyperosmolar coma,       |
|  |         | cardiovascular disease (e.g., heart    |
|  |         | disease, atherosclerosis,              |
|  |         | microvascular disease, hypertension,   |
|  |         | stroke, and other diseases and         |
|  |         | disorders as described in the          |
|  |         | "Cardiovascular Disorders" section     |
|  |         | below), dyslipidemia, endocrine        |
|  |         | disorders (as described in the         |
|  |         | "Endocrine Disorders" section          |
|  |         | below), neuropathy, vision             |
|  |         | impairment (e.g., diabetic retinopathy |
|  |         | and blindness), ulcers and impaired    |
|  |         | wound healing, infection (e.g.,        |
|  |         | infectious diseases and disorders as   |
|  |         | described in the "Infectious           |
|  |         | Diseases" section below (particularly  |
|  |         | of the urinary tract and skin). An     |

|    |         |     |                         |                                         | additional highly preferred indication  |
|----|---------|-----|-------------------------|-----------------------------------------|-----------------------------------------|
|    |         |     |                         |                                         | is obesity and/or complications         |
|    |         |     |                         |                                         | associated with obesity. Additional     |
|    |         |     |                         |                                         | highly preferred indications include    |
|    |         |     |                         |                                         | weight loss or alternatively, weight    |
|    |         |     |                         |                                         | gain. Additional highly                 |
|    |         |     |                         |                                         | preferred indications are               |
|    |         |     |                         |                                         | complications associated with insulin   |
|    |         |     |                         |                                         | resistance. Additional highly           |
|    |         |     |                         |                                         | preferred indications are disorders of  |
|    |         |     |                         |                                         | the musculoskeletal systems             |
|    |         |     |                         |                                         | including myopathies, muscular          |
|    |         |     |                         |                                         | dystrophy, and/or as described          |
|    |         |     |                         |                                         | herein. Additional highly               |
|    |         |     |                         |                                         | preferred indications include,          |
|    |         |     |                         |                                         | hypertension, coronary artery           |
|    |         |     |                         |                                         | disease, dyslipidemia, gallstones,      |
|    |         |     |                         |                                         | osteoarthritis, degenerative arthritis, |
|    |         |     |                         |                                         | eating disorders, fibrosis, cachexia,   |
|    |         |     |                         |                                         | and kidney diseases or disorders.       |
|    |         |     |                         |                                         | Preferred indications include           |
|    |         |     |                         |                                         | neoplasms and cancer, such as,          |
|    |         |     |                         |                                         | lymphoma, leukemia and breast,          |
|    |         |     |                         |                                         | colon, and kidney cancer. Additional    |
|    |         |     |                         |                                         | preferred indications include           |
|    |         |     |                         |                                         | melanoma, prostate, lung,               |
|    |         |     |                         |                                         | pancreatic, esophageal, stomach,        |
|    |         |     |                         |                                         | brain, liver, and urinary cancer.       |
|    |         |     |                         |                                         | Highly preferred indications include    |
|    |         |     |                         |                                         | lipomas and liposarcomas. Other         |
|    |         |     |                         |                                         | preferred indications include benign    |
|    |         |     |                         |                                         | dysproliferative disorders and pre-     |
|    |         |     |                         |                                         | neoplastic conditions, such as, for     |
|    |         |     |                         |                                         | example, hyperplasia, metaplasia,       |
|    |         |     |                         |                                         | and/or dysplasia.                       |
|    | HEPAB80 | 480 | Regulation of viability | Assays for the regulation of viability  | A highly preferred indication is        |
| 9/ |         |     | and proliferation of    | and proliferation of cells in vitro are | diabetes mellitus. An additional        |

| pancreatic beta cells. used or routinely modified to assess the ability of polypoptides of the white of the content of the polypoptides of the white of white of analysoms of the white white of the polypoptides of the white of polypoptides of the polypop |                       | highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic retinopathy, idiopathy, kidney disease (e.g., renal faillure, nephropathy and or other diseases and disorders as and or other diseases and disorders as | escribed in the Yealn Disorders'<br>section below), disbetic neuropathy,<br>were dissess and net row damage<br>(e.g., due to dishetic neuropathy),<br>duely devesable blockage, heart disease,<br>stroke, impotence (e.g., due to<br>stroke, impotence (e.g., due to<br>stroke, impotence (e.g., due to<br>hockage), sciences, mental<br>outlision, drowsiness, nonkeotic<br>outlision, drowsiness, nonkeotic<br>entition-acquit disease (e.g., heart<br>entition-acquit disease (e.g., heart<br>entition-acquit disease (e.g., heart                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | microvascular disease, harboratoriosa, microvascular disease, harboratoriosa, microvascular diseases and diseardes and educativas and educativas and educativas and educativas and proposition of the propo | and planiment (e.g., dithetic retinopubly and blindness), ulcers and impaired (e.g., mount belaing, and infection (e.g., infections diseases and disactorers as Diseases' section below, especially of the trimmy rare and skin), carpail under syndrome and Dayupereri secondary and populopus (e.g., An additional highly confered infections is obesity and/or complications associated with                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| prancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | pancratic beta cells. | well-known in the art and may be<br>used or routinely modificet to assess<br>the ability of polypeptides of the<br>invention (thedting antibodies and<br>agonists or antagonisis of the<br>invention) to regulate viability and                                      | but outlieration of protectable but edis.  For example, the Cell Titler-Gio missessen cell divisibility assay measures the number of visible cells measures the number of visible cells measures the number of visible cells the ATP present which signals the the ATP present which signals the the ATP present of metabolically active cells. Exemplary assays that may be used or noutinely medified to test used or noutinely medified to test present of protection of practice of the protection of practice of the cells protection of practice of the cells protection of practice of practice of the cells protection | including authorities and agonism on fundating authorities and agonism of including authorities and agonism on the anaethorises of the including and according a service disological in: Ohtani KI, et al., Endocrinology, 134(1):172-8 (1998); Kenuthein Ac et al. Engly 1172-8 (1998). Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in each of which is herein incorporated by reference.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | an entrey, Parentaire distinct may be used according to these may be used according to these may be used according to these moutinely generated. Exemplary paracretic cells that may be used according to these according to these according to these according to these according to the according to |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       | pancreatic beta cells.                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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|   |         |     |                                               | cells express [buegon, sornatoratin, and glucoordious The cells secrete insulin, which is cells secrete insulin, which is surface insulin, which is administed by glucose and glucose and glucoses diy sornatostatin or and suppressed by sornatostatin or glucoordiooids. ATIC4 (2R1777 Reis; Lord and Ashoroll. Biodochem. 1, 219; 547-551; Sainerre et al. Proc. 1981, and Acad. Sci. USA 78: 4339-4343, 1981.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | obesity. Additional highly preferred<br>distancions include weight loss or<br>alternatively, weight gain. Additional<br>thiply preferred indications are<br>complications associated with insulin<br>resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---|---------|-----|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| τ | HFABGI8 | 187 | Adirection of Adirection of Signaling Pathway | the country of the co | of the invention includes a method for stimulating adhocyte method for stimulating adhocyte method for stimulating adhocyte method included in a distriction of the stimulating adhocyte method for inhibiting adjucyte proliferation. A stifful preferred embediment of the inhibiting adjucycy proliferation. The stimulating adjucycy proliferation in the invention includes a method for inhibiting adjucycy edifferentiation. An alternative highly preferred embediment of the invention includes a method for inhibiting adjucycy edifferentiation. An alternative highly preferred embediment of the invention includes a method for inhibiting adjucyce differentiation. An alternative of the invention includes a method for inhibiting the advisoring of the advisoring of experience of the invention includes a method for invention includes as anchod of the invention includes as anchod of the invention includes as anchod of the invention includes as anchod of intention includes as anchod incl |
|   |         |     |                                               | MH, Prog Biophys Mol Biol 71(3-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Highly preferred indications also                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| include neoplastic diseases (e.g., lipomas, ilpostas, ilpostacomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension. | orongastive beart finature, blood vessel bloodage, heart disease, strike, impostence and/or so described below mader "Immune Activity", "Cardiovascular Diseades", and/or "Baode-Related Diseades", immune diseaders (e.g., as described below under "Immune Activity"), neural diseaders (e.g., as described below under "Immune Activity"), neural diseaders (e.g., as described below under "Immune Activity"), neural diseaders (e.g., as described below under "Mental Activity and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | infection (e.g., as described below<br>the when optical Diseases*), and<br>and marker and optical optical optical<br>A highly preferred indication is<br>highly preferred indication is<br>highly preferred indication. An additional<br>highly preferred indication is<br>highly preferred indication is<br>complication sociated with<br>disheric reprinopally, idiated, as a<br>function of the company of the company<br>of the company of the company of the company<br>and or other diseases and disorders as<br>section below), dishetic neuropathy,<br>and over diseases and three damage<br>(e.g., due to diahetic neuropathy),<br>servion below), dishetic neuropathy,<br>and over diseases and diseases,<br>servion below), dishetic neuropathy,<br>and over disease and disease,<br>servion below), dishetic neuropathy,<br>and over disease and disease,<br>servion below, dishetic neuropathy,<br>and over diseases and disease,<br>servion below, dishetic neuropathy,<br>and over diseases and disease,<br>servion below, disease, and the condition of the con-<br>clusion of the constant of the con-<br>dition of the constant of the con-<br>dition of the constant of the con-<br>dition of the con-<br>stant of the con-<br>traction of the |
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| 4).479-500 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g.,   | the through the ATC(Tv). Exemplary mouses adjrocyte cells that may be used according to these assays that discounting to these assays and the transfer of the | differentiation conditions known in the art.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly | preferred indications are | complications associated with insulin | resistance. Additional highly | preferred indications are disorders of | the musculoskeletal systems | including myopathies, muscular | ×. | herein. Additional highly | preferred indications include, | hypertension, coronary artery | disease, dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, | eating disorders, fibrosis, cachexia, |
|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|---------------------------------------|------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------|---------------------------|---------------------------------------|-------------------------------|----------------------------------------|-----------------------------|--------------------------------|----|---------------------------|--------------------------------|-------------------------------|------------------------------------|-----------------------------------------|---------------------------------------|
|                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |    |                           |                                |                               |                                    |                                         |                                       |
|                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |    |                           |                                |                               |                                    |                                         |                                       |
|                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |    |                           |                                |                               |                                    |                                         |                                       |

| Preferred indications include reposts and encey, sond its symptoma, trakenia and breast, unphonan, trakenia and breast, unphonan, trakenia and present additional postered indications include perferred indications include purchased, hing punctuals, esophiagail, sommer, punctuals, esophiagail, sommer, lightly preferred indications include braig preferred indications include braig preferred indications include braig preferred indications include braig methods to conditions, such as, for morphistic conditions, such as, for morphistic conditions, such as, for morphistic conditions, and and conditional and conditions include braig and conditions, such as, for morphistic conditions, such as, for method preparation of the preferred indications and conditions and conditions, such as, for method preferred indications and conditions, such as, for method preferred indications and conditions and conditions and conditions and conditions are conditions. | A highly perfected enbediment of the invention includes a method for maintaining endebtial teel growth. An alternative highly preferred combodinest of the invention includes a method for inhibiting emboducial cell growth. A highly preferred enhodiment of the invention includes a method for inhibiting endoducial cell growth. A highly perfected enhodivelial cell invention includes a method for animationic endoducial cell possible and the profile and the profil |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | cleanse Apoptosis Rescue. Assays<br>for caspace apoptosis rescue are well<br>brown in the art and may be used or<br>noutinely modified to assess the<br>ability of the polypeptides of the<br>ability of the polypeptides of the<br>ality of the polypeptides and agoniss or antagoniss of antibitic caspace<br>protease-mediated apoptosis.<br>Evernphira session for caspace<br>protease-mediated apoptosis.<br>Evernphira session for caspace<br>apoptosis that may be used or<br>noutively modified to test caspace<br>apoptosis rescue of polyperpides of<br>mixed the protection of the properties of<br>and agonists or antagonists of the<br>invention) include the assays<br>and agonists or antagonists of the<br>invention) include the assays<br>and agonists or antagonists of the<br>invention) include the assays<br>Res 45(5); 788-794 (2000). Messeme<br>Res 45(5); 788-794 (2000). Messeme<br>and agonist or antagonist or antagonist or antagonist<br>for any or antagonist or antagonist or antagonist or antagonist<br>for any or antagonist or any antagonist or antagonist or any<br>mixed and any antagonist or any any antagonist or any any any<br>and A athrecosker                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Protection from<br>Factorial Cell<br>Apoptosis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 188                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HFABGIS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| incon    | incorporated by reference in its      | preferred embodiment of the             |
|----------|---------------------------------------|-----------------------------------------|
| entire   | entirety. Endothelial cells that may  | invention includes a method for         |
| be us    | be used according to these assays are | stimulating apoptosis of endothelial    |
| Inpublic | publicly available (e.g., through     | cells. An alternative highly preferred  |
| comm     | commercial sources). Exemplary        | embodiment of the invention             |
| endot    | endothelial cells that may be used    | includes a method for inhibiting (e.g., |
| accor    | according to these assays include     | decreasing) apoptosis of endothelial    |
| bovin    | bovine aortic endothelial cells       | cells. A highly preferred               |
| (bAE     | (bAEC), which are an example of       | embodiment of the invention             |
| endot    | endothelial cells which line blood    | includes a method for stimulating       |
| vesse    | vessels and are involved in functions | angiogenisis. An alternative highly     |
| that ii  | that include, but are not limited to, | preferred embodiment of the             |
| angio    | angiogenesis, vascular permeability,  | invention includes a method for         |
| vascu    | vascular tone, and immune cell        | inhibiting angiogenesis. A highly       |
| extra    | extravasation.                        | preferred embodiment of the             |
|          |                                       | invention includes a method for         |
|          |                                       | reducing cardiac hypertrophy. An        |
|          |                                       | alternative highly preferred            |
|          |                                       | embodiment of the invention             |
|          |                                       | includes a method for inducing          |
|          |                                       | cardiac hypertrophy. Highly             |
|          |                                       | preferred indications include           |
|          |                                       | neoplastic diseases (e.g., as described |
|          |                                       | below under "Hyperproliferative         |
|          |                                       | Disorders"), and disorders of the       |
|          |                                       | cardiovascular system (e.g., heart      |
|          |                                       | disease, congestive heart failure,      |
|          |                                       | hypertension, aortic stenosis,          |
|          |                                       | cardiomyopathy, valvular                |
|          |                                       | regurgitation, left ventricular         |
|          |                                       | dysfunction, atherosclerosis and        |
|          |                                       | atherosclerotic vascular disease,       |
|          |                                       | diabetic nephropathy, intracardiac      |
|          |                                       | shunt, cardiac hypertrophy,             |
|          |                                       | myocardial infarction, chronic          |
|          |                                       | hemodynamic overload, and/or as         |
|          |                                       | described below under                   |

| - | 3        | "Cardiottaconlar Dicondore")            |
|---|----------|-----------------------------------------|
|   |          | Cardiovascular Disorders ).             |
|   | #_       | Highly preferred indications include    |
|   | 5        | cardiovascular, endothelial and/or      |
|   | ee       | angiogenic disorders (e.g., systemic    |
|   | P        | disorders that affect vessels such as   |
|   | P        | diabetes mellitus, as well as diseases  |
|   | •        | of the vessels themselves, such as of   |
|   | 7        | the arteries, capillaries, veins and/or |
|   |          | ymphatics). Highly preferred are        |
|   | ·ia      | indications that stimulate              |
|   | ë        | angiogenesis and/or                     |
|   | 5        | cardiovascularization. Highly           |
|   | 6.       | preferred are indications that inhibit  |
|   | 8        | angiogenesis and/or                     |
|   | 3        | cardiovascularization. Highly           |
|   | £.       | preferred indications include           |
|   | ie i     | antiangiogenic activity to treat solid  |
|   | #        | tumors, leukemias, and Kaposi"s         |
|   | 35       | sarcoma, and retinal disorders.         |
|   | H        | Highly preferred indications include    |
|   | 8        | neoplasms and cancer, such as,          |
|   | *        | Kaposi"s sarcoma, hemangioma            |
|   | <u> </u> | (capillary and cavernous), glomus       |
|   | <u> </u> | tumors, telangiectasia, bacillary       |
|   | e e      | angiomatosis,                           |
|   | 4        | hemangioendothelioma,                   |
|   | · B      | angiosarcoma,                           |
|   | <u>a</u> | haemangiopericytoma,                    |
|   |          | lymphangioma, lymphangiosarcoma.        |
|   | H        | Highly preferred indications also       |
|   | · ii     | include cancers such as, prostate,      |
|   | 4        | breast, lung, colon, pancreatic,        |
|   | 5        | esophageal, stomach, brain, liver,      |
|   | 8        | and urinary cancer. Preferred           |
|   | ii       | indications include benign              |
|   | P        | dysproliferative disorders and pre-     |
|   | a        | neoplastic conditions, such as, for     |

| _ |  | example, hyperplasia, metaplasia,      |
|---|--|----------------------------------------|
|   |  | and/or dysplasia, Highly               |
|   |  | preferred indications also include     |
|   |  | arterial disease, such as,             |
|   |  | atherosclerosis, hypertension,         |
|   |  | coronary artery disease,               |
|   |  | inflammatory vasculitides,             |
|   |  | Reynaud's disease and Reynaud's        |
|   |  | phenomenom, aneurysms, restenosis;     |
|   |  | venous and lymphatic disorders such    |
|   |  | as thrombophlebitis, lymphangitis,     |
|   |  | and lymphedema; and other vascular     |
|   |  | disorders such as peripheral vascular  |
|   |  | disease, and cancer. Highly            |
|   |  | preferred indications also include     |
|   |  | trauma such as wounds, burns, and      |
|   |  | injured tissue (e.g., vascular injury  |
|   |  | such as, injury resulting from balloon |
|   |  | angioplasty, and atheroschlerotic      |
|   |  | lesions), implant fixation, scarring,  |
|   |  | ischemia reperfusion injury,           |
|   |  | rheumatoid arthritis, cerebrovascular  |
|   |  | disease, renal diseases such as acute  |
|   |  | renal failure, and osteoporosis.       |
|   |  | Additional highly preferred            |
|   |  | indications include stroke, graft      |
|   |  | rejection, diabetic or other           |
|   |  | retinopathies, thrombotic and          |
|   |  | coagulative disorders, vascularitis,   |
|   |  | lymph angiogenesis, sexual             |
|   |  | disorders, age-related macular         |
|   |  | degeneration, and treatment            |
|   |  | /prevention of endometriosis and       |
|   |  | related conditions. Additional highly  |
|   |  | preferred indications include          |
|   |  | fibromas, heart disease, cardiac       |
|   |  | arrest, heart valve disease, and       |

| ad to attimore an attimore            | indications include autoimation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| agonesis or amagonists or an          | There are the state of the stat |
| invention) to mediate                 | disease (e.g., rheumatoid arthritis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| immunomodulation, regulate            | systemic lupus erythematosis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| inflammatory activities, modulate     | multiple sclerosis and/or as described                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| TH2 helper cell function, and/or      | below), immunodeficiency (e.g., as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| mediate humoral or cell-mediated      | described below), boosting a T cell-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| immunity. Exemplary assays that       | mediated immune response, and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| test for immunomodulatory proteins    | suppressing a T cell-mediated                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| evaluate the production of cytokines, | immune response. Additional highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| such as Interferon gamma (IFNg),      | preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| and the activation of T cells. Such   | inflammation and inflammatory                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| assays that may be used or routinely  | disorders. Additional preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| modified to test immunomodulatory     | indications include idiopathic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| activity of polypeptides of the       | pulmonary fibrosis. Highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| invention (including antibodies and   | preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| agonists or antagonists of the        | neoplastic diseases (e.g., leukemia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| invention) include the assays         | lymphoma, melanoma, and/or as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| disclosed in Miraglia et al., J       | described below under                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Biomolecular Screening 4:193-204      | "Hyperproliferative Disorders").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| (1999); Rowland et al.,               | Highly preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| "Lymphocytes: a practical approach"   | neoplasms and cancers, such as, for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Chapter 6:138-160 (2000); Gonzalez    | example, leukemia, lymphoma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| et al., J Clin Lab Anal 8(5):225-233  | melanoma, and prostate, breast, lung,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| (1995); Billiau et al., Ann NY Acad   | colon, pancreatic, esophageal,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Sci 856:22-32 (1998); Boehm et al.,   | stomach, brain, liver and urinary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Annu Rev Immunol 15:749-795           | cancer. Other preferred indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| (1997), and Rheumatology (Oxford)     | include benign dysproliferative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 38(3):214-20 (1999), the contents of  | disorders and pre-neoplastic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| each of which are herein              | conditions, such as, for example,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| incorporated by reference in its      | hyperplasia, metaplasia, and/or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| entirety. Human T cells that may be   | dysplasia. Preferred indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| used according to these assays may    | include anemia, pancytopenia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| be isolated using techniques          | leukopenia, thrombocytopenia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| disclosed herein or otherwise known   | Hodgkin's disease, acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| in the art. Human T cells are primary | lymphocytic anemia (ALL),                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| human lymphocytes that mature in      | plasmacytomas, multiple myeloma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| the thymus and express a T Cell       | Burkitt's lymphoma, arthritis, AIDS,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|    |         |     |                                       | receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preadivated to enhance responsiveness on immunomodulatory factors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | genulomatous disease, inflammatory bowel disease, spesis, neutropenia, neutopinia, psoriasis, suppression of immune reactions to transplanted ori grammate reactions to transplanted togens and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocardiris, mentingiisi. Lyme Disease, sastima and altergy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----|---------|-----|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 82 | HFABH95 | 482 | secretion from pancreatic beta cells. | instalin are well-known in the art and meaning secretion of missilin are well-known in the art and meaning by the great of the received by the great of the revention (including antibodies and agentists or mangonists of the invention) to stimulate instalin secretion. For example, instalin secretion for example, instalin secretion from panceratic beau is superglander by glucose and also by certain proteins/poptides, and edition for the supergland of its superglander by modified to test for stimulation of itsulin secretion from panceratic cells by polypeptides of the invention of instalin secretion including analysis disclosed in Ama I Physiol, 277(4 ft. 2) 8695466.  Am J Physiol, 277(4 ft. 2) 8695466.  Am J Physiol, 277(4 ft. 2) 87854564 (1997); Kim, Kim, Kitt., Elist. and all the secretion include and all the secretion of an analysis of the invention include and all the secretion of an analysis of the invention include and all the secretion of an analysis of the invention include and all the secretion of an analysis of the invention include and all the secretion of an analysis of the invention include and analysis of the invention of the invention include and analysis of the invention of | A highly preferred indication is diabetes mellins.  A highly preferred indication is a complication and preferred indication is a complication associated with diabetes (e.g., diabete retinopathy, diabetes to enphosphy; kidney disease (e.g., renal faiture, nephropathy and contections as and diseators as described in the 'Renal Disouders' section below, diabetes teaming the extended in the 'Renal Disouders' section below, diabetes to according to the order of the extended in the 'Renal Disouders' section below, disease, and carve diamage. The 'Renal Disouders' section below, disease, belocking, heart disease, heart disease, and contission, drowsites, mental contission, drowsites, mental contission, drowsites, mental contission, drowsites, mental contission, drowsites, and other diseases and calcusters and other diseases and engenesses. hypertension, endiovescular diseases and di |

| and wou infe desc desc Disc of th tumo cont tumo cont high and obes indicated associated | the FAS  A highly preferred indication is indicated with even features are well-known in additional lightly preferred indication used or rountiny;  sea complication associated with a care additional lightly preferred indication used or rountiny;  and agonitis or a complication associated with investion to reaction to make or the relation of the care of |
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| each of which is herein incomporated by reference in its entirety. Perceive in the entirety. Perceive cells that may be used according to these usesys are publishy available (e.g., through the ATCP-9) and/or may be used according to the sussys include art INS-1 cells. But may be used according to these assays include art INS-1 cells. But may be used according to these assays include art INS-1 cells. INS-1 cells. INS-1 cells are a semi-disting to these assays include art INS-1 cells. INS-1 cells are a semi-disting to these assays and a semi-disting to the entire continuous cells including glucose industrie training secretor.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Regulation of Assays for the regulation of Instanction through the FAS promoter element in hepatocytes the FAS promoter element in hepatocytes of the art and may be used or motified to assess the ability of polypergides of the invention of management of the invention of angeometral and to regulate the FAS promoter element in a sporter constants and to regulate the FAS promoter element in response to the FAS, a feet constrained by many transcription of FAS, a feet constrained by many transcription in regulated by many transcription in receives FAS gene unwarription in season and the FAS and the respirated by many transcription in receives FAS gene unwarription in show a summy transcription is also assemblant process dependent. Esemplary seasors that may be used                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 8 3 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HFALES77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| disease, atherosclerosis, microscalar disease, hypertension, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Jisoachers" section below). Avalitidenia and                           |                                                                                                                                                                                                                                                                                                                        | Diseases' section thelw, especially of the uninay tast and skin), carpal unmed syndrome and bupaytren's ournerates). An additional highly preferred indication is obesity. Additional highly preferred indication is obesity. Additional highly preferred indications include with obesity. Additional highly preferred alternatively, weight gain.  Additional highly preferred indications are complications in additional highly preferred indications are complications. | A highly perferred indication is a diabetes mellitus.  A highly perferred indication is a double of the perferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, lediney disease (e.g., renal failure, inephropathy and work or the disease and diseatories and described in the "Renal Disabeties and control education in the "Renal Disabeties and control education in the "Renal Disabeties and merce diseases and norre |
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| or routinely modified to test for FAS promote element activity (in hepatocytes) by polypepides of the invention (including antibodies and agonists or antagonists of the rivertion) include assays disclosed in remittin) include assays disclosed in | Xiong, S., et al., Proc Natl Acad Sci. 105.4, 97(8):286-53 (2000). Roder, K., et al., Eur J Brokem, Roder, K., et al., Eur J Brokem, B. St. (2007):743-51 (1930); Oskonian B. et al., Brokem, J. 317 (2017):27-65 (1996); Berger, et al., Gree 661-10 (1988); and, Cuttle, B., et al., Methods in Enzymol, 216:362-368 | is herein incorporated of which is herein incorporated by reference in its earliery. Hepatocytes that may be used according to these assays such as HHIE cells, are publicly available, est, through the ATTCVP3 and/or may be routinely generated.  The Exemplary hepotocytes that may be used according to these assays include and liver hepatoma cell line(s) include and liver hepatoma cell line(s) inducible with globocostroids, insiding, or cAMP derivatives.      | Assays for the regulation of ransacription of Malie Enzyme are well-known in the art and may be used or rentinely modified to assess the ability of polypeptides of the apility of polypeptides of the agonists or antagoniss or the agoniss or antagoniss of the agoniss or antagoniss of the factorion (to delighter transcription of Malie Enzyme, a key enzyme in Malie Enzyme, a key enzyme in involved in innecessisand its involved in innecessisand its                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Regulation of<br>transcription of Malic<br>Enzyme in adhocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 48.<br>48.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HFCEB37                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |         |     |                   | expression is stimulted by insulin.          | (e.g., due to diabetic neuropathy),    |
|----|---------|-----|-------------------|----------------------------------------------|----------------------------------------|
|    |         |     |                   | ME promoter contains two direct              | blood vessel blockage, heart disease,  |
|    |         |     |                   | repeat (DR1)- like elements MEp              | stroke, impotence (e.g., due to        |
|    |         |     |                   | and MEd identified as putative PPAR          | diabetic neuropathy or blood vessel    |
|    |         |     |                   | response elements. ME promoter               | blockage), seizures, mental            |
|    |         |     |                   | may also responds to AP1 and other           | confusion, drowsiness, nonketotic      |
|    |         |     |                   | transcription factors. Exemplary             | hyperglycemic-hyperosmolar coma,       |
|    |         |     |                   | assays that may be used or routinely         | cardiovascular disease (e.g., heart    |
|    |         |     |                   | modified to test for regulation of           | disease, atherosclerosis,              |
|    |         |     |                   | transcription of Malic Enzyme (in            | microvascular disease, hypertension,   |
|    |         |     |                   | adipoocytes) by polypeptides of the          | stroke, and other diseases and         |
|    |         |     |                   | invention (including antibodics and          | disorders as described in the          |
|    |         |     |                   | agonists or antagonists of the               | "Cardiovascular Disorders" section     |
|    |         |     |                   | invention) include assays disclosed          | below), dyslipidemia, endocrine        |
|    |         |     |                   | in: Streeper, R.S., et al., Mol              | disorders (as described in the         |
|    |         |     |                   | Endocrinol, 12(11):1778-91 (1998);           | "Endocrine Disorders" section          |
|    |         |     |                   | Garcia-Jimenez, C., et al., Mol              | below), neuropathy, vision             |
|    |         |     |                   | Endocrinol, 8(10):1361-9 (1994);             | impairment (e.g., diabetic retinopathy |
|    |         |     |                   | Barroso, I., et al., J Biol Chem,            | and blindness), ulcers and impaired    |
|    |         |     |                   | 274(25):17997-8004 (1999);                   | wound healing, and infection (e.g.,    |
|    |         |     |                   | Ijpenberg, A., et al., J Biol Chem,          | infectious diseases and disorders as   |
|    |         |     |                   | 272(32):20108-20117 (1997);                  | described in the "Infectious           |
|    |         |     |                   | Berger, et al., Gene 66:1-10 (1988);         | Diseases" section below, especially    |
|    |         |     |                   | and, Cullen, B., et al., Methods in          | of the urinary tract and skin), carpal |
|    |         |     |                   | Enzymol. 216:362-368 (1992), the             | tunnel syndrome and Dupuytren's        |
|    |         |     |                   | contents of each of which is herein          | contracture). An additional            |
|    |         |     |                   | incorporated by reference in its             | highly preferred indication is obesity |
|    |         |     |                   | entirety. Hepatocytes that may be            | and/or complications associated with   |
|    |         |     |                   | used according to these assays are           | obesity. Additional highly preferred   |
|    |         |     |                   | publicly available (e.g., through the        | indications include weight loss or     |
|    |         |     |                   | ATCC <sup>TM</sup> ) and/or may be routinely | alternatively, weight gain.            |
|    |         |     |                   | generated. Exemplary hepatocytes             | Aditional highly preferred             |
|    |         |     |                   | that may be used according to these          | indications are complications          |
|    |         |     |                   | assays includes the H4IIE rat liver          | associated with insulin resistance.    |
|    |         |     |                   | hepatoma cell line.                          |                                        |
|    | HFFAD59 | 485 | Regulation of     | Assays for the regulation of                 | A highly preferred indication is       |
| 81 |         |     | transcription via | transcription through the DMEF1              | diabetes mellitus. Additional highly   |
|    |         |     |                   | ,                                            |                                        |

| DMEF1 response        | response element are well-known in    | preferred indications include          |
|-----------------------|---------------------------------------|----------------------------------------|
| element in adipocytes | the art and may be used or routinely  | complications associated with          |
| and pre-adipocytes    | modified to assess the ability of     | diabetes (e.g., diabetic retinopathy,  |
|                       | polypeptides of the invention         | diabetic nephropathy, kidney disease   |
|                       | (including antibodies and agonists or | (e.g., renal failure, nephropathy      |
|                       | antagonists of the invention) to      | and/or other diseases and disorders as |
|                       | activate the DMEF1 response           | described in the "Renal Disorders"     |
|                       | element in a reporter construct (such | section below), diabetic neuropathy,   |
|                       | as that containing the GLUT4          | nerve disease and nerve damage         |
|                       | promoter) and to regulate insulin     | (e.g., due to diabetic neuropathy),    |
|                       | production. The DMEF1 response        | blood vessel blockage, heart disease,  |
|                       | element is present in the GLUT4       | stroke, impotence (e.g., due to        |
|                       | promoter and binds to MEF2            | diabetic neuropathy or blood vessel    |
|                       | transcription factor and another      | blockage), seizures, mental            |
|                       | transcription factor that is required | confusion, drowsiness, nonketotic      |
|                       | for insulin regulation of Glut4       | hyperglycemic-hyperosmolar coma,       |
|                       | expression in skeletal muscle.        | cardiovascular disease (e.g., heart    |
|                       | GLUT4 is the primary insulin-         | disease, atherosclerosis,              |
|                       | responsive glucose transporter in fat | microvascular disease, hypertension,   |
|                       | and muscle tissue. Exemplary assays   | stroke, and other diseases and         |
|                       | that may be used or routinely         | disorders as described in the          |
|                       | modified to test for DMEF1 response   | "Cardiovascular Disorders" section     |
|                       | element activity (in adipocytes and   | below), dyslipidemia, endocrine        |
|                       | pre-adipocytes) by polypeptides of    | disorders (as described in the         |
|                       | the invention (including antibodies   | "Endocrine Disorders" section          |
|                       | and agonists or antagonists of the    | below), neuropathy, vision             |
|                       | invention) include assays disclosed   | impairment (e.g., diabetic retinopathy |
|                       | in Thai, M.V., et al., J Biol Chem,   | and blindness), ulcers and impaired    |
|                       | 273(23):14285-92 (1998); Mora, S.,    | wound healing, and infection (e.g.,    |
|                       | et al., J Biol Chem, 275(21):16323-8  | infectious diseases and disorders as   |
|                       | (2000); Liu, M.L., et al., J Biol     | described in the "Infectious           |
|                       | Chem, 269(45):28514-21 (1994);        | Diseases" section below, especially    |
|                       | "Identification of a 30-base pair     | of the urinary tract and skin). An     |
|                       | regulatory element and novel DNA      | additional highly preferred indication |
|                       | binding protein that regulates the    | is obesity and/or complications        |
|                       | human GLUT4 promoter in               | associated with obesity. Additional    |
|                       | transgenic mice", J Biol Chem. 2000   | highly preferred indications include   |

| weight loss or alternatively, weight gain. Additional plaily performed gain. Additional plaily performs associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Preferred indicators include neophastic diseases (e.g., as described below under "Ippreprintferraive Disoactes"). Noted disorders (e.g., as described below under "Immune Activity", "Cardiovascular Activity", "Cardiovascular Activity", "Cardiovascular Activity", "Cardiovascular Activity", "Activity "Cardiovascular Activity", "Activity "Gardiovascular Activity", "Activity "Gardiovascular Activity", "Activity "Gardiovascular in mirecions disease as described below mirecions diseases as described below perferred indications include preferred indications include arthritis, systemic liquis preferred indications include arthritis, systemic liquis arthritis, systemic liquis arthritis and preferred indications include arthritis systemic liquis arthritis and preferred indications include arthritis systemic liquis arthritis and preferred indications include arthritis systemic liquis arthritis a |
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| Aug 4275(31):23666-73; Brager, et cl. Clare 66:110 (1988); and, cl. Clare 66:110 (1988); and concurs of each of which is herein concurs of each of which is herein propoprated by reference in its entirety. Adipocytes and prevence in centrety. Adipocytes and pray be used according to these issays are publicly and/or may be routinely generated. According to these issays are publicly and/or may be routinely generated. According to these issays are publicly and the property of the pro | transacription through the API and may be used or routinely modified to assess the ability of polypeytides of the invention) to polypeytides of the invention) to moditate growth and other celd furnitories. Exemplary assays for transacription through the API transacription and the api and a proper element and trainly of proposers element activity of properties of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transcription through transcription through API response element in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 485<br>485                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HFFADS9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|    |         |     |                                                                                               | and cheding an althodates and agoinsts or antagonists of the invention) include Gene 66:1-10 (1988), Callen and Man, Methods in Perger et al., Gene 66:1-10 (1988), Callen and Man, Methods in Pergyand 216:562-566 (1992); Hendmon et al., 1860 (1992); Hendmon et al., 1860 (1998); Relinkon et al., 1860 (1998); Allen et al., 1860 (1998); and Fraser et al. Part In Immorphy 20/5;388-44 (1999), the contents of each of which in its entirety. T cells that may be used sacording to these assays are publicly available et g., through the publicly available et g., through the publicly available et g., through the that may be used according to these assays include the CTLL cell line, which is m IL-2 dependent assays include in m IL-2 dependent assays encolume culture cell line with epotonoxic activity. | described below). Additional highly percented includes include the control of the |
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| 18 | HFFAD59 | 485 | Activation of transcription through serum response element in immune cells (such as T-cells). | Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| includes a method for stimulating<br>(e.g., increasing) TNF alpha<br>production. Preferred indications | include blood disorders (e.g., as<br>described below under "Immune<br>Activity", "Blood-Related          | Disorders", and/or "Cardiovascular<br>Disorders"), Highly preferred | indications include autoimmune<br>diseases (e.g., rheumatoid arthritis,       | systemic lupus erythematosis,          | croun's disease, intitupie seletosis<br>and/or as described below),         | immunodeficiencies (e.g., as        | described below), boosting a 1 cell-<br>mediated immune response, and | suppressing a T cell-mediated       | immune response. Additional highly | preferred indications include        | inflammation and inflammatory      | disorders, and treating joint damage | in patients with rheumatoid arthritis.  | An additional highly preferred | indication is sepsis. Highly         | preferred indications include  | neoplastic diseases (e.g., leukemia, | lymphoma, and/or as described         | below under "Hyperproliterative  | Disorders"). Additionally, highly | preferred indications include  | neoplasms and cancers, such as, for | example, leukemia, lymphoma, | melanoma, glioma (e.g., malignant | glioma), solid tumors, and prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver and<br>urinary cancer. Other preferred |
|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------|-------------------------------------|-----------------------------------------------------------------------|-------------------------------------|------------------------------------|--------------------------------------|------------------------------------|--------------------------------------|-----------------------------------------|--------------------------------|--------------------------------------|--------------------------------|--------------------------------------|---------------------------------------|----------------------------------|-----------------------------------|--------------------------------|-------------------------------------|------------------------------|-----------------------------------|--------------------------------------|----------------------------------|--------------------------------------------------------------------------|
| ability of polypeptides of the invention (including antibodies and agonists or antagonists of the      | invention) to regulate the serum<br>response factors and modulate the<br>expression of genes involved in | growth. Exemplary assays for<br>transcription through the SRE that  | may be used or routinely modified to<br>test SRE activity of the polypeptides | of the invention (including antibodies | and agonists or amagonists of the<br>invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in   Enzymol 216:362-368 (1992);             | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); and       | Black et al., Virus Genes 12(2):105- | 117 (1997), the content of each of | which are herein incorporated by     | reference in its entirety. T cells that | may be used according to these | assays are publicly available (e.g., | through the ATCC1M). Exemplary | mouse T cells that may be used       | according to these assays include the | CTLL cell line, which is an IL-2 | dependent suspension culture of T | cells with cytotoxic activity. |                                     |                              |                                   |                                      |                                  |                                                                          |
|                                                                                                        |                                                                                                          |                                                                     |                                                                               |                                        |                                                                             |                                     |                                                                       |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |                                |                                     |                              |                                   |                                      |                                  |                                                                          |
|                                                                                                        |                                                                                                          |                                                                     |                                                                               |                                        |                                                                             |                                     |                                                                       |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |                                |                                     |                              |                                   |                                      |                                  |                                                                          |
|                                                                                                        |                                                                                                          |                                                                     |                                                                               |                                        |                                                                             |                                     |                                                                       |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |                                |                                     |                              |                                   |                                      |                                  |                                                                          |

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| 83 | HFGAD82 | 486 | Activation of<br>transarytion through<br>API response element<br>in immune cells (such<br>as T-cells). | Assays for the activation of measurement of the mea | Preferred indications include the appliant Classes (e.g., as described below under Typoprolitientive Departed Sciences of Sciences of Sciences Sciences of Science |

|    |         |     |                                                                    | response element activity of oppoppulses of the invention (including antibodies and agonisis or authorities and agonisis or authorities and agonisis or authorities of the control of the | erythermatosis, multiple solerosis immunodeficiencies (e.g., sa dura is describe below), and immunodeficiencies (e.g., sa describe below). Additional highly preferred indications include inflammatory inflammatory disorders. Highly preferred inflammatory includes no billion includes on the complistic disorders (e.g., lenkemia, lymphoma, and/or sa described below under language of the complications also include modernes.) Highly preferred indications include and propassing and cancers, such as the lenkemia, lymphoma, prostatic, cleared indications include benign preferred indications multiply preferred indications include benign increasing objects of conditions, such as prepared conditions, such as prepared conditions, such as pre- pagested conditions, such as pre- pagested conditions, such as pre- complexed conditions, such as pre- complexed conditions, such as pre- |
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|    |         |     |                                                                    | veryoning to these assays include the HTZ cell line, which is an ILL4 dependent suspension culture cell line that also responds to ILL4.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | indications include arthritis, asthma, and originals, asthma, and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 82 | HFGAD82 | 486 | Stimulation of insulin<br>secretion from<br>pancreatic beta cells. | Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | A highly preferred indication is<br>diabetes mellitus. An<br>additional highly preferred indication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| _                                     | _                                     | _                                    | _                                 | _                                      | _                                  | _                                    | _                                      | _                                   | _                                      | _                                   | _                                   |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     | _                                    | _                                      | _                                    | _                                      | _                                   | _                                 |                                        |                                      | _                                    |
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| is a complication associated with     | diahetes (e.g., diahetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | discase, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious           | Discases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture). An additional       | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred |
| assess the ability of polypeptides of | the invention (including antibodies   | and agonists or antagonists of the   | invention) to stimulate insulin   | secretion. For example, insulin        | secretion is measured by FMAT      | using anti-rat insulin antibodies.   | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S et. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | are a semi-adherent cell line        | established from cells isolated from |
|                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |
|                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |
|                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |

| indications include weight loss or<br>alternatively, weight gain.<br>Actitional highly preferred<br>indications are complications<br>associated with insulin resistance.                                                          | diabetes mellins, An additional highly proferred indication is a complexion associated with diabetes mellins, An additional highly proferred indication is a complexion associated with diabetes neglinopathy, beiney disease, ce.g., retail failure, nephropathy and do or their disease and diseaders as described in the "Realal Disorders" according blook, placetic neuropathy, nerve diseases and nerve damage (e.g., due to diabetic neuropathy, hence a complexity of the professional and a contract disease, and the contract disease, and the contract of the programmers, imported (e.g., due to diabetic neuropathy or blood vessel bloodegs), sectures, mental confission, drowsiteres, nontral diseases, afterosederosis, including the programmers of the programm |
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| an X-ray induced rat transplantable insulinoura. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al., Endocrinology 1992 130-167. | and proliferation of cells in vitro and proliferation of cells in vitro and relation in the art and may be and or routinely modified to assess the ability of polypeptides of the removino (theologing authorities and agoniss or antagoniss or antagoniss or antagoniss of antagoniss of the provincion (theologing authorities and agoniss or antagoniss of the provincion of pancreatic beta cells, brothering to the cell riter-(4 to be example, the Cell Titer-(4 to be example to be example to the cells Exempleary sassys flat may be used or routinely modified to test regulation of vitability and the continuous of the invention include antagonists of the invention include is becein inconported by reference in chain kit, the section inconported by reference in cells that in the beautiful to the section to expect the cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                   | Regulation of violity and polification of puraveatic beat cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                   | 888                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                   | HFTURRIO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                   | 26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| wound healing, and infection (e.g., infections season disorders as described in the "Infections Sussess and disorders as described in the "Infections Sussess" section below, especially of the urinary tract and skin), carpain under syndrome and Dispoylers is contractured. An additional highly preferred indication is obesity and/or obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional indictions include weight loss or alternatively, weight gain. Additional indications include weight loss or alternatively, weight gain. Additional complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | A highly profited emboliment of the invention includes a method for stimulating adhocyte prolifection. An alternative highly preferred emboliment of the prolifection. An alternative highly preferred emboliment of the inhibiting adhocyte prolifectation. An alternative prolifectation of the invention includes a method for inhibiting adjocyce prolifectation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adjocyce differentiation. An alternative highly preferred modification includes a method for inhibiting adjocyce differentiation. An alternative highly preferred embolimen of the invention includes a method for inhibiting adjocyce differentiation. A manufacture of the invention includes a method for inhibiting adjocyce differentiation. A manufacture of the invention includes a method for inhibiting adjocyce activation. An alternative includes a method for any anticontain and alternative includes a method for alternative includes a meth |
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| ussays are publicly available (e.g., methodi the ACCO) and/or may be routinely generated. Exemplary parential cells that may be tassed according to these assays include according to these assays include the according to these assays include and adherent spilled from Syrian humster islet established from Syrian humster is established from Syrian humster is all the case of the state of the | the continue assay, for the complex and Elle I kinnse assay, for ERK Sgrad transduction that regulate cell poliferation or differentiation are viel known in the art and may be and rounding thought so the seases the ability of polypoptides of the removine (including anthodies and agoniss or antagoniss of other differentiation. Exemplary assays for ERK kinnse activity that may be used or monitoridy modified to test ERK kinnse activity that may be used or monitoridy modified to test ERK conduction of the invention of polypoptides of the invention of polypoptides of the invention of conduction and the polypoptides of the invention includes and agoniss or antagoniss of the invention including amploties and agonisis or antagoniss of the invention including amploties and agonisis or antagonis of the invention including                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| [                                        | ļ.                               |                                                                        |                                 |                                     |                                   | _                                   |                                  |                                   |                                    |                                 |                                  |                                      | P                                   |                                      | sel                                         |                                   | MΟ                                 |                                    | Ä                                  | nne                                   |                                     |                                      | _                                   |                              |                                     |                                     |                              |                                  | nal                |                                  |                              | _^                                    | ase                                  |                                   | s as                                   | _                                  |
|------------------------------------------|----------------------------------|------------------------------------------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|---------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|---------------------------------------------|-----------------------------------|------------------------------------|------------------------------------|------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|--------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|
| diment of                                | outliett of the                  | nemod for                                                              | activating                      | Highly preferred                    | ndocrine                          | cribed belov                        | orders").                        | cations also                      | cases (e.g.,                       | s, and/or as                    | и                                | Disorders").                         | include bloc                        | tension,                             | re, blood ve                                | se, stroke,                       | lescribed bel                      | /ity",                             | rders", and/e                      | rders"), imm                          | cribed belov                        | rity"), neural                       | cribed belov                        | ty and                       | s"), and                            | cribed below                        | ease").                      | dication is                      | An additional      | ation is a                       | ed with                      | c retinopathy                         | , kidney dise                        | phropathy                         | and disorder                           | al Disorders                       |
| of the transferred compositions of their | reierred entre                   | invention includes a method for<br>inhibiting the activation of (e.g., | decreasing) and/or inactivating |                                     | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | nclude neoplastic diseases (e.g.,  | ipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders")      | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel      | olockage, heart disease, stroke,  | mpotence and/or as described below | inder "Immune Activity"            | 'Cardiovascular Disorders", and/or | 'Blood-Related Disorders"), immune    | disorders (e.g., as described below | inder "Immune Activity"), neural     | lisorders (e.g., as described below | inder "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | inder "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" |
| highly                                   | mgm .                            | inhihitin                                                              | decreasi                        | adipocytes.                         | indicatic                         | disorder                            | under "E                         | Highly F                          | include                            | lipomas,                        | describe                         | "Hyperp                              | Ргебетте                            | disorder                             | congesti                                    | blockage                          | impoten                            | under "I                           | "Cardio                            | "Blood-                               | disorder                            | under "I                             | disorder                            | under "♪                     | Neurolo                             | infection                           | under "I                     | A highly                         | diabetes           | highly p                         | complic                      | diabetes                              | diabetic                             | (е.g., гет                        | and/or o                               | describe                           |
| lo to ac                                 | 10 4.,                           | el Y. Exn                                                              |                                 | riakis JM,                          | 18 (1999);                        |                                     | d Cobb                           | 171(3-                            | ents of                            |                                 | ıits                             | cells that                           | iese                                | e (e.g.,                             | mplary                                      | nay be                            | ıys                                | L1 is an                           | te cell                            | strain of                             | eq                                  | undergo                              | ike                                 | ie.                          | nown in                             |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
| and in Lone                              | Sect 111 FOLD                    | hand-Brist                                                             | Diabetes                        | (1999); Kyı                         | mp 64:29-4                        | , Nature                            | (2001); an                       | ys Mol Bio                        | 9); the cont                       | e herein                        | reference ir                     | adipocyte                            | ording to th                        | sly available                        | CTM). Exe                                   | cells that r                      | o these assa                       | cells. 3T3-                        | preadipocy                         | tinuous sub                           | ells develop                        | solation and                         | to adipose-l                        | r appropria                  | onditions kr                        |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
| of the second disclosed in Lounnes of of | nie assays msciosed in rollel et | Biol Chem 3/3(8-9):1101-1110<br>(1998): Le Marchand-Bristel Y. Exn     | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein        | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ). Exemplary | mouse adipocyte cells that may be | used according to these assays     | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | ine that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | ť                                   |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
| thon                                     | a chi                            | 1990                                                                   | Clin                            | 107(                                | Bioch                             | Chan                                | 410(                             | MH,                               | 4):47                              | each                            | incor                            | entire                               | may                                 | assay                                | thron                                       | mons                              | pasn                               | inch                               | adhe                               | line t                                | 3T3                                 | thron                                | a pre                               | conv                         | differ                              | the art                             |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        | _                                  |
|                                          |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
|                                          |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
|                                          |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
| L                                        |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
|                                          |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
| L                                        |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
|                                          |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |
| L                                        |                                  |                                                                        |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                             |                                   |                                    |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |

|  |  | section below), diabetic neuropathy.   |
|--|--|----------------------------------------|
|  |  | nerve disease and nerve damage         |
|  |  | (e.g., due to diabetic neuropathy),    |
|  |  | blood vessel blockage, heart disease,  |
|  |  | stroke, impotence (e.g., due to        |
|  |  | diabetic neuropathy or blood vessel    |
|  |  | blockage), seizures, mental            |
|  |  | confusion, drowsiness, nonketotic      |
|  |  | hyperglycemic-hyperosmolar coma,       |
|  |  | cardiovascular disease (e.g., heart    |
|  |  | disease, atherosclerosis,              |
|  |  | microvascular disease, hypertension,   |
|  |  | stroke, and other diseases and         |
|  |  | disorders as described in the          |
|  |  | "Cardiovascular Disorders" section     |
|  |  | below), dyslipidemia, endocrine        |
|  |  | disorders (as described in the         |
|  |  | "Endocrine Disorders" section          |
|  |  | below), neuropathy, vision             |
|  |  | impairment (e.g., diabetic retinopathy |
|  |  | and blindness), ulcers and impaired    |
|  |  | wound healing, infection (e.g.,        |
|  |  | infectious diseases and disorders as   |
|  |  | described in the "Infectious           |
|  |  | Diseases" section below (particularly  |
|  |  | of the urinary tract and skin). An     |
|  |  | additional highly preferred indication |
|  |  | is obesity and/or complications        |
|  |  | associated with obesity. Additional    |
|  |  | highly preferred indications include   |
|  |  | 100                                    |
|  |  | gain. Additional highly                |
|  |  | preferred indications are              |
|  |  | complications associated with insulin  |
|  |  | resistance. Additional highly          |
|  |  | preferred indications are disorders of |
|  |  | the musculoskeletal systems            |

|    |         |     |                   |                                        | including myopathies, muscular          |
|----|---------|-----|-------------------|----------------------------------------|-----------------------------------------|
|    |         |     |                   |                                        | dystrophy, and/or as described          |
|    |         |     |                   |                                        | herein. Additional highly               |
|    |         |     |                   |                                        | preferred indications include,          |
|    |         |     |                   |                                        | hypertension, coronary artery           |
|    |         |     |                   |                                        | disease, dyslipidemia, gallstones,      |
|    |         |     |                   |                                        | osteoarthritis, degenerative arthritis, |
|    |         |     |                   |                                        | eating disorders, fibrosis, cachexia,   |
|    |         |     |                   |                                        | and kidney diseases or disorders.       |
|    |         |     |                   |                                        | Preferred indications include           |
|    |         |     |                   |                                        | neoplasms and cancer, such as,          |
|    |         |     |                   |                                        | lymphoma, leukemia and breast,          |
|    |         |     |                   |                                        | colon, and kidney cancer. Additional    |
|    |         |     |                   |                                        | preferred indications include           |
|    |         |     |                   |                                        | melanoma, prostate, lung,               |
|    |         |     |                   |                                        | pancreatic, esophageal, stomach,        |
|    |         |     |                   |                                        | brain, liver, and urinary cancer.       |
|    |         |     |                   |                                        | Highly preferred indications include    |
|    |         |     |                   |                                        | lipomas and liposarcomas. Other         |
|    |         |     |                   |                                        | preferred indications include benign    |
|    |         |     |                   |                                        | dysproliferative disorders and pre-     |
|    |         |     |                   |                                        | neoplastic conditions, such as, for     |
|    |         |     |                   |                                        | example, hyperplasia, metaplasia,       |
|    |         |     |                   |                                        | and/or dysplasia.                       |
|    | HFTBM50 | 490 | Insulin Secretion | Assays for measuring secretion of      | A highly preferred indication is        |
| 98 |         |     |                   | insulin are well-known in the art and  | diabetes mellitus. An additional        |
|    |         |     |                   | may be used or routinely modified to   | highly preferred indication is a        |
|    |         |     |                   | assess the ability of polypeptides of  | complication associated with            |
|    |         |     |                   | the invention (including antibodies    | diabetes (e.g., diabetic retinopathy,   |
|    |         |     |                   | and agonists or antagonists of the     | diabetic nephropathy, kidney disease    |
|    |         |     |                   | invention) to stimulate insulin        | (e.g., renal failure, nephropathy       |
|    |         |     |                   | secretion. For example, insulin        | and/or other diseases and disorders as  |
|    |         |     |                   | secretion is measured by FMAT          | described in the "Renal Disorders"      |
|    |         |     |                   | using anti-rat insulin antibodies.     | section below), diabetic neuropathy,    |
|    |         |     |                   | Insulin secretion from pancreatic beta | nerve disease and nerve damage          |
|    |         |     |                   | cells is upregulated by glucose and    | (e.g., due to diabetic neuropathy),     |
|    |         |     |                   | also by certain proteins/peptides, and | blood vessel blockage, heart disease,   |

| _ |  | disregulation is a key component in    | stroke, impotence (e.g., due to        |
|---|--|----------------------------------------|----------------------------------------|
|   |  | diabetes. Exemplary assays that may    | diabetic neuropathy or blood vessel    |
|   |  | be used or routinely modified to test  | blockage), seizmes, mental             |
|   |  | for stimulation of insulin secretion   | confusion, drowsiness, nonketotic      |
|   |  | (from pancreatic cells) by             | hyperglycemic-hyperosmolar coma,       |
|   |  | polypeptides of the invention          | cardiovascular disease (e.g., heart    |
|   |  | (including antibodies and agonists or  | disease, atherosclerosis,              |
|   |  | antagonists of the invention) include  | microvascular disease, hypertension,   |
|   |  | assays disclosed in: Shimizu, H., et   | stroke, and other diseases and         |
|   |  | al., Endocr J, 47(3):261-9 (2000);     | disorders as described in the          |
|   |  | Salapatek, A.M., et al., Mol           | "Cardiovascular Disorders" section     |
|   |  | Endocrinol, 13(8):1305-17 (1999);      | below), dyslipidemia, endocrine        |
|   |  | Filipsson, K., et al., Ann N Y Acad    | disorders (as described in the         |
|   |  | Sci, 865:441-4 (1998); Olson, L.K.,    | "Endocrine Disorders" section          |
|   |  | et al., J Biol Chem, 271(28):16544-    | below), neuropathy, vision             |
|   |  | 52 (1996); and, Miraglia S et. al.,    | impairment (e.g., diabetic retinopathy |
|   |  | Journal of Biomolecular Screening,     | and blindness), ulcers and impaired    |
|   |  | 4:193-204 (1999), the contents of      | wound healing, and infection (e.g.,    |
|   |  | each of which is herein incorporated   | infectious diseases and disorders as   |
|   |  | by reference in its entirety.          | described in the "Infectious           |
|   |  | Pancreatic cells that may be used      | Diseases" section below, especially    |
|   |  | according to these assays are publicly | of the urinary tract and skin), carpal |
|   |  | available (e.g., through the ATCCTM)   | tunnel syndrome and Dupuytren's        |
|   |  | and/or may be routinely generated.     | contracture). An additional            |
|   |  | Exemplary pancreatic cells that may    | highly preferred indication is obesity |
|   |  | be used according to these assays      | and/or complications associated with   |
|   |  | include HITT15 Cells. HITT15 are       | obesity. Additional highly preferred   |
|   |  | an adherent epithelial cell line       | indications include weight loss or     |
|   |  | established from Syrian hamster islet  | alternatively, weight gain. Additional |
|   |  | cells transformed with SV40. These     | highly preferred indications are       |
|   |  | cells express glucagon, somatostatin,  | complications associated with insulin  |
|   |  | and glucocorticoid receptors. The      | resistance.                            |
|   |  | cells secrete insulin, which is        |                                        |
|   |  | stimulated by glucose and glucagon     |                                        |
|   |  | and suppressed by somatostatin or      |                                        |
|   |  | glucocorticoids. ATTC# CRL-1777        |                                        |
|   |  | Refs: Lord and Ashcroft. Biochem.      |                                        |

|                                                                                        | Highly perfect moterois include allergy and stilma. Additional highly perfect directions include immune and hematopolici diseased; (e.g., se describe below under "Humme Activity", and "Blood" "Humme Activity", and "Blood diseases (e.g., rehumsnois deribinis systemic library excrydentanis); systemic library excrydentanis; Cohn's disease, miliple scirosis and/or as described below). Immunodifications (e.g., at Cell-mediated below), boosting, at Cell-mediated below), and suppressing at Teell-mediated minimuse response, and suppressing at Teel-mediated minimuse response.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| J. 219; 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | activation of T-cells are well known in the art and may be tased or notatinely modified to assess the articles of modified to assess the article of additional and articles of the articles of the articles of T-cells. Exempting assess that articles of the invention (mothality articles) to the articles of the invention (mothality and articles of the invention) to modified to assist the articles of the properties and articles of the invention (mothality and articles of the invention) to modified to appear to the proposition and or T-cell in Edwards of the invention of modified in the invention of the article articles are articles. The article article articles are articles are articles are articles are articles. The article articles are contained to a many be used according to these assessing articles. The Cells are a class of activation. The cells are are also as of the factors that industres. |
|                                                                                        | Production of L-10 and activation of T-cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                        | 900                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                        | H- IBANDO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                        | 98                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|                                                                                                                                                                                                                                                                                                                         | the invention includes a method for members of highly preferred embodiment of healthy medicals call growth. An alternative highly preferred members in the properties of the process of th |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| differentiation and activation of Th2  regist play a migor role in the initiation and publogenesis of allergy and asthina. Prinary T helper 2  cells are generated via in vitro culture under Th2 polarizing conditions under Th2 polarizing conditions is assignerable-all flowed ymphosyres isolated from ored blood. | for esepace, apoptosis rescue. Assury<br>for esepace, apoptosis rescue are well<br>for esepace, apoptosis rescue are well<br>where the properties of the<br>rescue in the standard and the best of the<br>ability of the polypeptides of the<br>ability of the polypeptides of the<br>apoptosis that are the properties of the<br>rescue of the ability of the polypeptides of<br>the rescue of the ability of the ability of the<br>proposis that may be used to<br>apoptosis that may be used to<br>the rescue of polypeptides of<br>the rescue of polypeptides of the<br>apoptosis rescue of polypeptides of<br>apoptosis rescue of polypeptides of<br>the rescue of polypeptides of<br>and agonists or attagentias of the<br>mercation include the tassity<br>disclosed in Romeo et al., Candowase<br>Res 4(3): 788-74 (2000), Messure<br>et al., Br. J Pharmacol 1277): 1633-<br>for the proposition of the proposition of the pro-<br>ference of each of which are herein<br>incorporated by reference in its<br>energy. Endodrish cells that may be used<br>commercial sources). Exemplant<br>commercial sources). Exemplant<br>encodediated cells that may be used<br>according to these assays are                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                         | Protection from Tandersial Cell Apoptosis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                         | 164                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                         | HFTD236                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                         | £8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| 4        | bovine aortic endothelial cells                                       | cells. A highly preferred                                        |
|----------|-----------------------------------------------------------------------|------------------------------------------------------------------|
| = 5      | (DAEC), which are an example of<br>endothelial cells which line blood | embodiment of the invention<br>includes a method for stimulating |
|          | vessels and are involved in functions                                 | angiogenisis. An alternative highly                              |
| =        | that include, but are not limited to,                                 | preferred embodiment of the                                      |
| <u> </u> | angiogenesis, vascular permeability,                                  | oc.                                                              |
|          | vascular tone, and immune cell                                        | inhibiting angiogenesis. A highly                                |
| <u> </u> | extravasation.                                                        | preferred embodiment of the                                      |
|          |                                                                       | invention includes a method for                                  |
|          |                                                                       | reducing cardiac hypertrophy. An                                 |
|          |                                                                       | alternative highly preferred                                     |
|          |                                                                       | embodiment of the invention                                      |
|          |                                                                       | includes a method for inducing                                   |
|          |                                                                       | cardiac hypertrophy. Highly                                      |
|          |                                                                       | preferred indications include                                    |
|          |                                                                       | neoplastic diseases (e.g., as described                          |
|          |                                                                       | below under "Hyperproliferative                                  |
|          |                                                                       | Disorders"), and disorders of the                                |
|          |                                                                       | cardiovascular system (e.g., heart                               |
|          |                                                                       | disease, congestive heart failure,                               |
|          |                                                                       | hypertension, aortic stenosis,                                   |
|          |                                                                       | cardiomyopathy, valvular                                         |
|          |                                                                       | regurgitation, left ventricular                                  |
|          |                                                                       | dysfunction, atherosclerosis and                                 |
|          |                                                                       | atherosclerotic vascular disease,                                |
|          |                                                                       | diabetic nephropathy, intracardiac                               |
|          |                                                                       | shunt, cardiac hypertrophy,                                      |
|          |                                                                       | myocardial infarction, chronic                                   |
|          |                                                                       | hemodynamic overload, and/or as                                  |
|          |                                                                       | described below under                                            |
|          |                                                                       | "Cardiovascular Disorders").                                     |
|          |                                                                       | Highly preferred indications include                             |
|          |                                                                       | cardiovascular, endothelial and/or                               |
|          |                                                                       | angiogenic disorders (e.g., systemic                             |
|          |                                                                       | disorders that affect vessels such as                            |
|          |                                                                       | diabetes mellitus, as well as diseases                           |
|          |                                                                       | of the vessels themselves, such as of                            |

| _ | the arteries        | the arteries, capillaries, veins and/or |
|---|---------------------|-----------------------------------------|
|   | Iymphatics          | lymphatics). Highly preferred are       |
|   | indications         | indications that stimulate              |
|   | angiogenesis and/or | sis and/or                              |
|   | cardiovasci         | cardiovascularization. Highly           |
|   | preferred at        | preferred are indications that inhibit  |
|   | angiogenesis and/or |                                         |
|   | cardiovasci         | cardiovascularization. Highly           |
|   | preferred in        | preferred indications include           |
|   | antiangioge         | antiangiogenic activity to treat solid  |
|   | tumors, leu         | tumors, leukemias, and Kaposi"s         |
|   | sarcoma, ar         | sarcoma, and retinal disorders.         |
|   | Highly pref         | Highly preferred indications include    |
|   | neoplasms           | neoplasms and cancer, such as,          |
|   | Kaposi's sa         | Kaposi"s sarcoma, hemangioma            |
|   | (capillary a        | (capillary and cavernous), glomus       |
|   | tumors, tela        | tumors, telangiectasia, bacillary       |
|   | angiomatosis,       | sis,                                    |
|   | hemangioer          | hemangioendothelioma,                   |
|   | angiosarcoma,       | ima,                                    |
|   | haemangior          | haemangiopericytoma,                    |
|   | lymphangic          | lymphangioma, lymphangiosarcoma.        |
|   | Highly pref         | Highly preferred indications also       |
|   | include can         | include cancers such as, prostate,      |
|   | breast, lung        | breast, lung, colon, pancreatic,        |
|   | esophageal          | esophageal, stomach, brain, liver,      |
|   | and urinary         | and urinary cancer. Preferred           |
|   | indications         | indications include benign              |
|   | dysprolifera        | dysproliferative disorders and pre-     |
|   | neoplastic          | neoplastic conditions, such as, for     |
|   | example, hy         | example, hyperplasia, metaplasia,       |
|   | and/or dysp         | and/or dysplasia. Highly                |
|   | preferred in        | preferred indications also include      |
|   | arterial dise       | arterial disease, such as,              |
|   | atherosclere        | atherosclerosis, hypertension,          |
|   | coronary ar         | coronary artery disease,                |
|   | inflammato          | inflammatory vasculitides,              |

|  |  | Revnaud"s disease and Revnaud"s        |
|--|--|----------------------------------------|
|  |  | phenomenom, aneurysms, restenosis;     |
|  |  | venous and lymphatic disorders such    |
|  |  | as thrombophlebitis, lymphangitis,     |
|  |  | and lymphedema; and other vascular     |
|  |  | disorders such as peripheral vascular  |
|  |  | disease, and cancer. Highly            |
|  |  | preferred indications also include     |
|  |  | trauma such as wounds, burns, and      |
|  |  | injured tissue (e.g., vascular injury  |
|  |  | such as, injury resulting from balloon |
|  |  | angioplasty, and atheroschlerotic      |
|  |  | lesions), implant fixation, scarring,  |
|  |  | ischemia reperfusion injury,           |
|  |  | rheumatoid arthritis, cerebrovascular  |
|  |  | disease, renal diseases such as acute  |
|  |  | renal failure, and osteoporosis.       |
|  |  | Additional highly preferred            |
|  |  | indications include stroke, graft      |
|  |  | rejection, diabetic or other           |
|  |  | retinopathies, thrombotic and          |
|  |  | coagulative disorders, vascularitis,   |
|  |  | lymph angiogenesis, sexual             |
|  |  | disorders, age-related macular         |
|  |  | degeneration, and treatment            |
|  |  | /prevention of endometriosis and       |
|  |  | related conditions. Additional highly  |
|  |  | preferred indications include          |
|  |  | fibromas, heart disease, cardiac       |
|  |  | arrest, heart valve disease, and       |
|  |  | vascular disease. Preferred            |
|  |  | indications include blood disorders    |
|  |  | (e.g., as described below under        |
|  |  | "Immune Activity", "Blood-Related      |
|  |  | Disorders", and/or "Cardiovascular     |
|  |  | Disorders"). Preferred indications     |
|  |  | include autoimmune diseases (e.g.,     |

|    |         |     |                       | et al., FEBS Lett, 377(2):237-9        | disorders (as described in the         |
|----|---------|-----|-----------------------|----------------------------------------|----------------------------------------|
|    |         |     |                       | (1995); and, Miraglia S et. al.,       | "Endocrine Disorders" section          |
|    |         |     |                       | Journal of Biomolecular Screening,     | below), neuropathy, vision             |
|    |         |     |                       | 4:193-204 (1999), the contents of      | impairment (e.g., diabetic retinopathy |
|    |         |     |                       | each of which is herein incorporated   | and blindness), ulcers and impaired    |
|    |         |     |                       | by reference in its entirety.          | wound healing, and infection (e.g.,    |
|    |         |     |                       | Pancreatic cells that may be used      | infectious diseases and disorders as   |
|    |         |     |                       | according to these assays are publicly | described in the "Infectious           |
|    |         |     |                       | available (e.g., through the ATCCTM)   | Diseases" section below, especially    |
|    |         |     |                       | and/or may be routinely generated.     | of the urinary tract and skin), carpal |
|    |         |     |                       | Exemplary pancreatic cells that may    | me a                                   |
|    |         |     |                       | be used according to these assays      | contracture). An additional            |
|    |         |     |                       | include rat INS-1 cells. INS-1 cells   | highly preferred indication is obesity |
|    |         |     |                       | are a semi-adherent cell line          | and/or complications associated with   |
|    |         |     |                       | established from cells isolated from   | obesity. Additional highly preferred   |
|    |         |     |                       | an X-ray induced rat transplantable    | indications include weight loss or     |
|    |         |     |                       | insulinoma. These cells retain         | alternatively, weight gain.            |
|    |         |     |                       | characteristics typical of native      | Aditional highly preferred             |
|    |         |     |                       | pancreatic beta cells including        | indications are complications          |
|    |         |     |                       | glucose inducible insulin secretion.   | associated with insulin resistance.    |
|    |         |     |                       | References: Asfari et al.              |                                        |
|    |         |     |                       | Endocrinology 1992 130:167.            |                                        |
|    | HFXBL33 | 492 | Regulation of         | Assays for the regulation of           | A highly preferred indication is       |
| 88 |         |     | transcription via     | transcription through the DMEF1        | diabetes mellitus. Additional highly   |
|    |         |     | DMEF1 response        | response element are well-known in     | preferred indications include          |
|    |         |     | element in adipocytes | the art and may be used or routinely   | complications associated with          |
|    |         |     | and pre-adipocytes    | modified to assess the ability of      | diabetes (e.g., diabetic retinopathy,  |
|    |         |     |                       | polypeptides of the invention          | diabetic nephropathy, kidney disease   |
|    |         |     |                       | (including antibodies and agonists or  | (e.g., renal failure, nephropathy      |
|    |         |     |                       | antagonists of the invention) to       | and/or other diseases and disorders as |
|    |         |     |                       | activate the DMEF1 response            | described in the "Renal Disorders"     |
|    |         |     |                       | element in a reporter construct (such  | section below), diabetic neuropathy,   |
|    |         |     |                       | as that containing the GLUT4           | nerve disease and nerve damage         |
|    |         |     |                       | promoter) and to regulate insulin      | (e.g., due to diabetic neuropathy),    |
|    |         |     |                       | production. The DMEF1 response         | blood vessel blockage, heart disease,  |
|    |         |     |                       | element is present in the GLUT4        | stroke, impotence (e.g., due to        |
|    |         |     |                       | promoter and binds to MEF2             | diabetic neuropathy or blood vessel    |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | A highly preferded embodiment of the invention includes a method for simulating adjrosyte a method for simulating adjrosyte an embod profiferation. An alternative highly preferred embodiment of the inhibiting adjrosyte proliferation. A highly preferred embodiment of the invention includes a method for inhibiting adjrosyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adjrosyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting and previous includes a method for inhibiting the activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the advention includes a method for internative highly preferred embodiment of the invention includes a method for internative highly preferred embodiment of the invention includes a method for internative highly preferred indications include endocrine indicators (e.g., see searched below under "Endocrine Disorders").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| mouse 3T3-L1 cell line which is an memorae 3T3-L1 cell line which is an inferent money preading-occell line. Mouse 3T3-L1 cells are a continuous substant no 3T3 incholass developed through closed incholass developed through closed sudency appraisant. These cells undergo a pravailantion. These cells undergo a pravailantion. These cells undergo a pravailantion continue and proposition adjocas-like conversion culture appropriate differentiation culture conditions. | centrage and It-Li kines assays, for exemple an It-Li kines assays, for a filter seasy. Strikes assays, for exemple an It-Li kines assays, for exemple an It-Li kines assays, for exemple and interest and may be used are rounthey and different and may be used are rounthey and different assays in the allity of polyperpidies of the metarotto (including ambidoiss and agontists or amagonisis of the proliferention, activation, and may be used the control to the correlation and are assays for PRK kinese activity dust may be used the control the control to the control of the con |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Adriocyte ERK Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 493                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | HFXIIK73                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | **                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders").              | Preferred indications include blood<br>disorders (e.g., hypertension,<br>congestive heart failure, blood vessel       | blockage, heart disease, stroke,<br>impotence and/or as described below | under "Immune Activity", "Cardiovascular Disorders", and/or "Blood Delated Disorders", immune              | disorders (e.g., as described below | disorders (e.g., as described below | under "Neural Activity and<br>Neurological Diseases") and           | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | dica | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease<br>(e \sigma renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma,<br>cardiovascular disease (e.g. heart |
|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------------------------------------|-------------------------------------|------------------------------|----------------------------------|------|------------------------------|---------------------------------------|------------------------------------------------------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|------------------------------------------------------------------------|
| each of which are herein<br>incorporated by reference in its<br>entirety. Mouse adipocyte cells that | may be used according to these<br>assays are publicly available (e.g.,<br>through the ATCC <sup>TM</sup> ). Exemplary | mouse adipocyte cells that may be<br>used according to these assays     | include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of | 3T3 fibroblast cells developed      | a pre-adipocyte to adipose-like     | conversion under appropriate<br>differentiation conditions known in | the art.                            |                              |                                  |      |                              |                                       |                                                                              |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                                                        |
|                                                                                                      |                                                                                                                       |                                                                         |                                                                                                            |                                     |                                     |                                                                     |                                     |                              |                                  |      |                              |                                       |                                                                              |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                                                        |
|                                                                                                      |                                                                                                                       |                                                                         |                                                                                                            |                                     |                                     |                                                                     |                                     |                              |                                  |      |                              |                                       |                                                                              |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                                                        |
|                                                                                                      |                                                                                                                       |                                                                         |                                                                                                            |                                     |                                     |                                                                     |                                     |                              |                                  |      |                              |                                       |                                                                              |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                                                        |

|  | disease athemsolemsis                   |
|--|-----------------------------------------|
|  | concern concerns.                       |
|  | microvascular disease, hypertension,    |
|  | stroke, and other diseases and          |
|  | disorders as described in the           |
|  | "Cardiovascular Disorders" section      |
|  | below), dyslipidemia, endocrine         |
|  | disorders (as described in the          |
|  | "Endocrine Disorders" section           |
|  | below), neuropathy, vision              |
|  | impairment (e.g., diabetic retinopathy  |
|  | and blindness), ulcers and impaired     |
|  | wound healing, infection (e.g.,         |
|  | infectious diseases and disorders as    |
|  | described in the "Infectious            |
|  | Diseases" section below (particularly   |
|  | of the urinary tract and skin). An      |
|  | additional highly preferred indication  |
|  | is obesity and/or complications         |
|  | associated with obesity. Additional     |
|  | highly preferred indications include    |
|  | weight loss or alternatively, weight    |
|  | gain. Additional highly                 |
|  | preferred indications are               |
|  | complications associated with insulin   |
|  | resistance. Additional highly           |
|  | preferred indications are disorders of  |
|  | the musculoskeletal systems             |
|  | including myopathies, muscular          |
|  | dystrophy, and/or as described          |
|  | herein. Additional highly               |
|  | preferred indications include,          |
|  | hypertension, coronary artery           |
|  | disease, dyslipidemia, gallstones,      |
|  | osteoarthritis, degenerative arthritis, |
|  | eating disorders, fibrosis, cachexia,   |
|  | and kidney diseases or disorders.       |
|  | Preferred indications include           |

| adinocyte differentiation A       | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a<br>complication associated with |
|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|----------------------------------|------------------------------------------------------------------|
| or routinely modified to test ERK | kinasa-induced activity of         | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                                  |                                                                  |
|                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                                                  |
|                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                                                  |

| diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight |
|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|---------------------------------------|------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|
|                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |
|                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |
|                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |

|    |         |     |                                                                                             |                                                                                                                                                                                                                                                                | repetred infections such as the resistance and additional lighty preferred infections are disorders of the resistance.  Additional lighty preferred infections are disorders of the misculosalected is yearn the misculosalected is yearn the misculosalected is yearn disorders of the misculosalected is yearn disorders of the properties, miscular disorders and or as feet-med infectional highly preferred infections include disorders, dispetal stomethy preferred infections include melanom, prostate, lung melanom, dipositions include informs and inpostrooms. Other informs and inpostrooms. Other informs and inpostrooms. Other informs and inpostrooms. Other observed infections is such as, for example, hyporphist, metalplasia, metalplasia, |
|----|---------|-----|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 | HFXKY27 | 495 | Activation of transcription through GAS response clement in immune cells (such as T-cells). | Assays for the activation of remarging the Gamma Interaction to the activation Site (GAS) response clearization Site (GAS) response clearization size (CAS) modified to assess the ability of puppetizes of the invention (including antibodies and agoniss or | Highly preferred indications Highly preferred indications Highly preferred indications leader reoplastic diseases (e.g., lenkernia lymphoma, and/or as described below under described below under Highly preferred indications include Highly preferred indications include example, lenkernia lymphoma (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|    |                 |     |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | pareytopenia, letakopenia, letakopenia, letakopenia, letakopenia, acute lymphocyte anemia (ALL), demaneytomas, anthiple myolona, arthritis, Allys, grandomatous educases, indumentory bowd disease, seepsis, neutuopiliti, powradis, suppression of immue reactions to transplanted organs and issues, hemophilia, to consoplated organs and issues, hemophilia, to the constitution of the compiliar, condocardisi, meningilis, Lyme endocardisis, meningilis, Lyme |
|----|-----------------|-----|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 92 | <b>Н</b> СВН135 | 496 | inhibitor of squalenc<br>synthense gene<br>transcription.          | Reporter Assay: construct contains sequelation yand coulon sequence of squalence working sequence of squalence synthesise, the first specific experime in the challestern of the challes | Discuss, and astima and aitergy.                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 92 | новніз5         | 496 | Stimulation of insulin<br>secretion from<br>pancreatic beta cells. | Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonisis or anagonisis of the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabete (e.g., diabetic retinopathy, idiabetic replicapathy, kidney disease.                                                                                                                                                                                                                                                         |

| invention) to stimulate insulin secretion from partnership invention) to stimulate insulin secretion from panerentic between comparation of diabetes. Exempler in the standard of institution is a key cortain protein-speptides, and between comparation of a street in the containing the standard of insulin secretion from panerentic orbits and problems and agonise of the mercanic from panerentic orbits and agonise of the mercanic methodics and agonise of the mercanic orbits and agonise of the mercanic methodics and agonise of the mercanic methodics and agonise of the mercanic orbits and agonise or an agonic orbits and agonise of the mercanic orbits and agonise or an agonic orbits and agonic orbits and agonic orbits and agonic orbits agonic orbits and agonic orbits and agonic orbits agonic orbits and agonic orbits ag | où.                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                      | . >                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| invention) to stimulate insulin secretion is measured by PMAT susing and an attainin antibodic beat cells in progradued by PMAT susing and an attainin antibodic beat cells in sprogradued by PMAT susing and an attainin antibodic beat cells in sprogradued by BMAT susing and an attainin antibodic beat cells in sprogradued by BMAT susing and an attainin antibodic beat cells in the cells of the ce |                                                                                                                                                                                     | ege, due to dichetto neuropathy),<br>hond vessel hockage, heart disease<br>strone, imponence (e.g., due to<br>dishecio neuropathy or blood vessel<br>blockage), sectures, mental<br>comfision, thouseness, montal<br>or confision, thouseness, montale<br>hyperglyvennic-hyperoxamolar count<br>through and disease (e.g., heart<br>disease, adrenoscirronis.                                        | incrovascular diseases, hypertension<br>stroke, and other diseases and diseases and<br>strokes, and other diseases and<br>"Cardiovascular Disorders" section<br>below), dyslipidemia, endocrane<br>below), pushipidemia, endocrane<br>"Endocrine Disorders" section<br>below), neuropathy, vision<br>impairment (e.g., diabetic retinopath<br>impairment (e.g., diabetic retinopath |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | invention) to stimulate insulin<br>secretion. For example, insulin<br>secretion is measured by FMAT<br>using anti-rat insulin antibodies.<br>Insulin secretion from pancreatic beta | also by certain potentise personal and also by certain potentise/perpities, and exequation is a key component in disbetes. Exempliny assisy that may be used or rotainely modified to test of seinfuldation of insulin secretion (from parecente cells) by the unique of the invention (mon parecente cells) by the invention (melluding ambodies and agoniss or concluding ambodies and agonises or | anagonisto (in hrvention) include<br>assays disclosed in Almen, B., et al.,<br>Am Physio, 2774 Pt. 21899-66<br>(1999); Li. M. et al. Endocrinology<br>(1809); 275-40 (1997); Knn, K.H.<br>(1995); and, Mraglis Sc. al.,<br>(1995); and, Mraglis Sc. al.,<br>(1995); and, Mraglis Sc. al.,<br>(1995); and (1994), the contents of                                                    | and not which is herein incorporated<br>by reference in its entirety.  Parcratic cells that may be used<br>coording to these assays are publicly<br>available (e.g., through the ATCCP9)<br>and or may be noturited generated.  Exemplary panereatic cells that may<br>include an INS1 cells. INS1, cells<br>are a semi-adherent cell line<br>are a semi-adherent cell sine are<br>an X-ray induced rat transplantable<br>an area with the second retain<br>characteristics typical of induve |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|   |         |     |                     | pancreatic beta cells including glucose inducible insulin secretion.  References: Asfari et al.  Endocrinology 1992 130:167.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | indications are complications<br>associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---|---------|-----|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8 | HGLAF75 | 497 | Emzentation of Male | transcription of Malei Enzyme are wastern for the regulation of Transcription of Malei Enzyme are wastern with the Malei Enzyme are wastern for the Malei Enzyme are wastern of including ambacies and against or amagonis or amagonis of the malei or properties of the manufol or together curyme is involved in hipogenesis Malei curyme, a key orazyme in involved in hipogenesis and integrated the area of the Malei Enzyme, a key orazyme in involved in hipogenesis and malei orazyme is involved in hipogenesis and malei or and the area of the manufol or together with a malei or an adversario and the cleament Malei and Malei dentified as putative PPAR and other may also responds to API and other may be used or routinely or the control of | A highly preferred indication is diachees nedlins and didictional highly perceraed indication and deditional highly perceraed indication is a complication associated with diachees (e.g., diabetic retinopathy, distoy disease (e.g., renal indiace, nephropathy and distorted in the formal Disorders's and disorders as described in the 'Renal Disorders's active of the formal Disorders's care the object to enumpathy or blood vessel blocking, heart diseases, and only disorders active importance (e.g., due to dishefter neuropathy or blood vessel blocking, heart diseases, mental contision, drowsiness, mortal contision, drowsiness, horselforms's, microry active and prefer incisence of disorders with diseases and disorders's section below), dyslindernia, endocrine disorders's section below), dyslindernia, endocrine disorders's section impairment (e.g., diabetic entempaphy vision impairment (e.g., diabetic entempaphy vision heart propriets and princess) and inferences in direction of a forest and inferior of a forest and a forest and propriets. |
|   |         |     |                     | Ijpenberg, A., et al., J Biol Chem,<br>272(32):20108-20117 (1997);                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | infectious diseases and disorders as<br>described in the "Infectious                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| Diseases' section below, especially the the training and the training training and Dappytons is construction. An additional lightly preferred indication is obesity and complications associated with obesity. Additional highly preferred districtions indications in short weight loss or alternatively, weight gain obesity, Additional highly preferred alternatively, weight gain alternatively, weight gain indications indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                               | diabetes mellins. An additional is additional highly proterred and diabetes mellins. An additional complete processed indication is a complication associated with a diabetes (e.g., diabetic reinopolity, kidney diabetic repiropolity, nerve diseases and dareve diamage (e.g., the to diabetic neuropality), however, importney (e.g., due to diabetic neuropality) blood vessel blokegae, heart diseases, mental contrision, drowsiness, mental contri                                                                                                                                                                                           |
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| Berger, et al., Gene 66:1-10 (1988), and Culton, p. et al., Mednok in Braymol. 216:46:3-86 (1992), the contents of et al. of the contents of et al. of which is herein morphorated by reference in its neutral Hendrocket Braymol. 1992, the used according to these assays are pused according to these assays are pushely availor may be rouninely ATCCPs) and/or may be rouninely and/or may be rouninely and/or may be used according to these assays includes the mouse 313-L1 cell line. 373-L1 is a mouse preadip-cope cell line (adherent). It is a normation sushiner in G1333 including a parallipopular cell line (adherent). It is a nontimous assays includes the mouse 313-L1 submitted and proposed through chand all and admitted as pure additions, cliffs our conversation and all procyte to adipose-like conversation culture conditions. | and proliferation of cells in vitro me<br>and proliferation of cells in vitro me<br>used or routinely modified to assess<br>used or routinely modified to assess<br>the ability of popypridics of the<br>agonists or antagonists of this and<br>agonists or antagonists of this and<br>proliferation of patterwish beat cells,<br>from the cell filed city<br>from the cell filed city<br>from the cell filed city<br>from the cell filed city<br>from the cell filed city<br>in offline based on quantitation of<br>presence of metabolically active<br>presence of metabolically active<br>pre |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | and position of viability and positions of viability and positions of pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 497                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HGLAF75                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 86                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|    |         |     |                   | regulation of viability and policitation of production to profice and a production for budding analysis and against the including analysis and against on anaequoists of the invention) include anaequoists of the invention) include a supersy disclosed in: Friedrichaen IN, et al., Mol Indocrinol, 15(1):36–48 (1998); Ingal SR, et al., J Diot Chem 1998); Ingal SR, et al., J Diot Chem 1998); Ingal SR, et al., J Diot Chem 1998; Ingal SR, et al., J Diot Chem incorporately preference in its entirety. Pancreatic cells that may be contacts of each of which is instructive collection of the seasons are publicly available (e.g., frought the convented of reference in the convention of the seasons are publicly available (e.g., frought the convented of Ectoroparts or the convented or the convent | hyperglycemic-hyperoxinolar count, activities and sease (e.g., heart disease, atheroxicorasis, disease, hypertension, stroke, and other diseases, hypertension, stroke, and other diseases and "Cardiovascular Diseaders as described in the "Cardiovascular Disarders' section diseases and diseases and diseases (see described in the "Fatocrine Disarders' section diseased, described in the "Fatocrine Disarders' section diseased, activities (e.g., diabetic retinopathy and behanders), thouse and impaured wound healing, and infection (e.g., diabetic retinopathy activities and single diseased section behave appearing to the professional processes and disarders as described in the "Infections  or and setal series and described in the "Infections are and setal series are all described in the "Infections" or and setal series are described in the "Infections" or and setal series are described in the "Infections" or and setal series are described in the "Infections" or and setal series are distincted as a described in the "Infections" or and setal series are distincted as a described in the "Infections" or an activity or |
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|    |         |     |                   | cells that may be toold according to<br>cells that may be toold according to<br>INST cells. In Self-cells.<br>INST cells may semi-adherent cell<br>from an Azay induced rat<br>remaplanable insulinoma. These<br>cells team characteristics spiral of<br>the properties of the properties of the<br>cells team characteristics spiral of<br>the properties of the cells including<br>glucose influcible mailin secution.<br>Factories: Asid in et al.<br>Factories: Asid in et al.<br>Factories and acception.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | tumed syndrome and Dippoytera's accommendation and additional highly preferred influential resolutions are solutionally and preferred influential resolutions are solution to obesity. Additional highly preferred midditional highly preferred alternatively, weight gain. Additional alternatively, weight gain. Additional highly preferred indications are larger and alternatively, weight gain. Additional highly preferred indications are complications associated with instilling resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 93 | HGLAF75 | 497 | Insulin Secretion | A ssays for measuring secucion of<br>insulin are vell-krown in the art and<br>may be used or routinely modified in<br>seases the ability of polypeptides of<br>the invention (including authodics<br>and agoniss or antigonists of the<br>invention) to simulate insulin<br>secretion. For example, insulin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | heighty preferred indication is disheren self-indicational highly preferred indications is a roughlest on seasonated with disheren e.g., disheric retinopathy, indirects (e.g., disheric retinopathy, kidney disease (e.g., renal liniure, methropathy and/or other diseases and diseases.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage  | (e.g., due to diabetic neuropany),<br>blood vessel blockage, heart disease,<br>stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel<br>blockage), seizures, mental<br>confusion, drowsiness, nonketotic              | hyperglycemic-hyperosmolar coma,<br>cardiovascular disease (e.g., heart | disease, atherosclerosis,<br>microvascular disease hypertension                | stroke, and other diseases and       | ansorders as described in the<br>"Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the<br>"Endocrine Disorders" section            | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy<br>and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as<br>described in the "Infections | Discases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's      | ed ir                               | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or<br>alternatively, weight gain, Additional | highly preferred indications are   | complications associated with insulin | resistance.                       |
|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------|-------------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|------------------------------------------------------------------------------|------------------------------------|---------------------------------------|-----------------------------------|
| secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta | cens is upregulated by guicose and also by certain proteins/peptides, and disregulation is a key component in  | diabetes. Exemplary assays that may<br>be used or routinely modified to test<br>for stimulation of insulin secretion | (from pancreatic cells) by                                              | (including antibodies and agonists or<br>antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000);<br>Salapatek, A.M., et al., Mol  | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad<br>Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S et. al.,<br>Journal of Biomolecular Screening,     | 4:193-204 (1999), the contents of   | each of which is herein incorporated<br>by reference in its entirety | Pancreatic cells that may be used   | according to these assays are publicly | available (e.g., through the ATCCTM) | Exemplary pancreatic cells that may | be used according to these assays    | include HITF15 Cells. HITT15 are     | an adnerent epimenal cen ime<br>established from Svrian hamster islet        | cells transformed with SV40. These | cells express glucagon, somatostatin, | and glucocorticoid receptors. The |
|                                                                                                         |                                                                                                                |                                                                                                                      |                                                                         |                                                                                |                                      |                                                                     |                                   |                                                                            |                                     |                                                                               |                                     |                                                                      |                                     |                                        |                                      |                                     |                                      |                                      |                                                                              |                                    |                                       |                                   |
|                                                                                                         |                                                                                                                |                                                                                                                      |                                                                         |                                                                                |                                      |                                                                     |                                   |                                                                            |                                     |                                                                               |                                     |                                                                      |                                     |                                        |                                      |                                     |                                      |                                      |                                                                              |                                    |                                       |                                   |

| HHRCs30 | 408             | Ariteation of                     | is almost a processing the processing and suppressed by sometical in processing the processing and suppressed by sometical in or proceedings of the processing and shitten in the processing the processing and shitten in the processing and shitten in the processing and processing and processing and processing the processing processing and processing processing and processing processing and processing proce | A highly preferred enhodimon                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| 2       | 80 <del>0</del> | Adipoyte ERK<br>Signaling Pathway | commple an Elel. Kinnes assay, for the chance assay, for the Res grant translation that regulate cell polification of differentiation cell polification of differentiation and the act and may be used or rountinely modified to assass the ability of polyperplicies of the invention (including unbedies and agontiss or antagoniss or the invention of tending to the polyperplicies of the polyficentiation. Levernplant seasons for extension of the committee of the polyperplicies of the invention or crimible to the ERK kinase activity that may be used the fifth of the polyperplicies of the invention include to testing the invention include the assays disclosed in Forter et al. (1998); Le Amerimach-Brack and Chan 7940-291 [101-110]. (1998); Le Amerimach-Brackers (1999); Kraikis M. Biochem Soc Symp 64/2948 (1999).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | of the invention includes a method for the invention includes a method for simulating applicacyte proliferation. An alternative highly perfected embediation of the invention includes a method for intubilities adjacogyte proliferation. In inhibiting adjacogyte proliferation in inhibiting adjacogyte proliferation of the invention includes a method for inhibiting adjacogyte differentiation. An alternative bighty preferred embediation of the invention includes a method for inhibiting and proposed differentiation. An alternative highly preferred embediation of the highly preferred embediation. An alternative highly preferred embediation, an alternative highly preferred embediation of the inhibiting the activation of metivating addiscussion studies endowned addiscussion studies endowned indications include endowned medications include endowned proposed and proposed propos |
|         |                 |                                   | MH, Prog Biophys Mol Biol 71(3-<br>4):479-500 (1999); the contents of<br>each of which are herein                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| er                               | Disorders").                         | include blood                       | rension,                             | are, blood vessel                      | se, stroke,                       | described below                     | vity",                             | orders", and/or                    | rders"), immune                        | scribed below                       | vity"), neural                       | scribed below                       | ity and                      | es"), and                           | scribed below                       | sease").                     | dication is                      | An additional      | cation is a                      | ted with                     | ic retinopathy,                       | , kidney disease                     | ephropathy                        | and disorders as                       | nal Disorders"                     | tic nemopathy,                       | rve damage                     | neuropathy),                       | e, heart disease,                     | g., due to                      | or blood vessel                     | mental                      | ss, nonketotic                    | rosmolar coma,                   | se (e.g., heart                     | 010                     |
|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|--------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|-------------------------|
| described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity"            | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy) | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | dispase atherocolerosis |
| incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     | _                       |
|                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |
|                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                    |                                       |                                 |                                     |                             |                                   |                                  |                                     |                         |

|  |  | microvascular disease hynertension      |
|--|--|-----------------------------------------|
|  |  | ottoolea and other discourse and        |
|  |  | stroke, and other diseases and          |
|  |  | disorders as described in the           |
|  |  | "Cardiovascular Disorders" section      |
|  |  | below), dyslipidemia, endocrine         |
|  |  | disorders (as described in the          |
|  |  | "Endocrine Disorders" section           |
|  |  | below), neuropathy, vision              |
|  |  | impairment (e.g., diabetic retinopathy  |
|  |  | and blindness), ulcers and impaired     |
|  |  | wound healing, infection (e.g.,         |
|  |  | infectious diseases and disorders as    |
|  |  | described in the "Infectious            |
|  |  | Diseases" section below (particularly   |
|  |  | of the urinary tract and skin). An      |
|  |  | additional highly preferred indication  |
|  |  | is obesity and/or complications         |
|  |  | associated with obesity. Additional     |
|  |  | highly preferred indications include    |
|  |  | weight loss or alternatively, weight    |
|  |  | gain. Additional highly                 |
|  |  | preferred indications are               |
|  |  | complications associated with insulin   |
|  |  | resistance. Additional highly           |
|  |  | preferred indications are disorders of  |
|  |  | the musculoskeletal systems             |
|  |  | including myopathies, muscular          |
|  |  | Š                                       |
|  |  | herein. Additional highly               |
|  |  | preferred indications include,          |
|  |  | hypertension, coronary artery           |
|  |  | disease, dyslipidemia, gallstones,      |
|  |  | osteoarthritis, degenerative arthritis, |
|  |  | eating disorders, fibrosis, cachexia,   |
|  |  | and kidney diseases or disorders.       |
|  |  | Preferred indications include           |
|  |  | neoplasms and cancer, such as,          |

|    |         |     |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | on, and skinge enter. Additional preferred infectations include preferred infectations include perferred infectations include penceratic scophageal, stomach penceratic scophageal, stomach entin liver, and trainay cancer. Highly preferred infectations include inportations include inportations include benigm observed infectations include benigm dyspositic conditions, such as, for example, hyporphisa, metaplasia, newtons, example, in-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----|---------|-----|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 96 | HHBCS39 | 498 | TNFa in Human T-cell<br>2B9        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 8  | HHEAA08 | 499 | Adjivoyte ERK<br>Signaling Pathway | ceample an Ele. Kinnes assay, for example an Ele. Kinnes assay, for the Res ignal transpaction that regulate cell positivement of the cell most of the cell mos | A highly perferred embodiment of the invention includes a method free invention includes a method proliferation An alternative highly preferred embodiment of the inthiting adjacopy as a method for inthiting adjacopy embodiment of the invention includes a method for inthiting adjacopy proliferation. An alternative highly preferred the invention includes a method for includes a method for thinhibing the invention includes a method for includes an enthod for inhibiting highly preferred embodiment of the invention includes a method of includes a method for inhibiting adjacopyte differentiation. An alternative highly preferred embodiment of the invention includes a method for includes a method of an inhibiting adjacopyte activation. An alternative adjacopyte activation. An alternative includes as method of the invention includes a method for invention includes a method for invention includes a method for invention includes a method of or invention includes a method or invention includes a method of or invention incl |

| is JM, adipocytes. Highly preferred (1999); indications include endocrine disorders (e.g., as described below obb under "Endocrine Disorders").                            | . a                                                                                                                                                                                            | , a %                                                                                                                                                                                                                                                                                          | n in                                                                                                                                                        | described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), shoot useed blockene heart itsease. |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (1070); 126-132 (1999); Kyriakis JM,<br>Biochem Soe Symp 6:129-48 (1999);<br>Chang and Karin, Mature<br>(106824); 37-40 (2001); and Cob<br>MH Proce Biochem Med Biol 2117. | 4),479,500 (1993), the contents of each of which are bretin incorporated by reference in its entirety. Mouse adhocyte cells that may be used according to these may be used according to these | through the ATC(270). Exemplies through the ATC(270). Exemplies more earliesty or cells that may be used according to these assays inched FTAL list and adherent mouse preadlepseyle cell in the first is confinitions between 43T fithrobiast cells developed 13T fithrobiast cells developed | through doub is baisinion and undergo<br>a pre-adipocyte to adipose-like<br>conversion under appropriate<br>differentiation conditions known in<br>the art. |                                                                                                                                                                                |
|                                                                                                                                                                            |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                |                                                                                                                                                             |                                                                                                                                                                                |

|  |  | stroke, innotence (e.g., due to        |
|--|--|----------------------------------------|
|  |  | disheric neuronathy or blood yessel    |
|  |  | blockers) cairmed mental               |
|  |  | blockage), seizines, mentai            |
|  |  | confusion, drowsmess, nonketotic       |
|  |  | hyperglycemic-hyperosmolar coma,       |
|  |  | cardiovascular disease (e.g., heart    |
|  |  | disease, atherosclerosis,              |
|  |  | microvascular disease, hypertension,   |
|  |  | stroke, and other diseases and         |
|  |  | disorders as described in the          |
|  |  | "Cardiovascular Disorders" section     |
|  |  | below), dyslipidemia, endocrine        |
|  |  | disorders (as described in the         |
|  |  | "Endocrine Disorders" section          |
|  |  | below), neuropathy, vision             |
|  |  | impairment (e.g., diabetic retinopathy |
|  |  | and blindness), ulcers and impaired    |
|  |  | wound healing, infection (e.g.,        |
|  |  | infectious diseases and disorders as   |
|  |  | described in the "Infectious           |
|  |  | Diseases" section below (particularly  |
|  |  | of the urinary tract and skin). An     |
|  |  | additional highly preferred indication |
|  |  | is obesity and/or complications        |
|  |  | associated with obesity. Additional    |
|  |  | highly preferred indications include   |
|  |  | los                                    |
|  |  | gain. Additional highly                |
|  |  | preferred indications are              |
|  |  | complications associated with insulin  |
|  |  | resistance. Additional highly          |
|  |  | preferred indications are disorders of |
|  |  | the musculoskeletal systems            |
|  |  | including myopathies, muscular         |
|  |  | dystrophy, and/or as described         |
|  |  | herein. Additional highly              |
|  |  | preferred indications include,         |

| _                                                                |                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |
|------------------------------------------------------------------|----------------------------------------|-------------------------------------|---------------------------------|----------------------------------------|---------------------------------|----------------------------------------|----------------------------------|-----------------------------------|-------------------------------------|-------------------------------|--------------------------------------|------------------------------------|------------------------------------|--------------------------------------|--------------------------------|--------------------------------------|--------------------------------------|----------------------------------------|----------------------------------|-------------------------------------|----------------------------------|---------------------------------------|------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-------------------------------------|------------------------------|-------------------------------------|--------------------------------|--------------------------------|-----------------------|----------------------------------------|-----------------------------------|---------------------------------------|
| embodiment of the invention<br>includes a method for inhibiting  | adipocyte proliferation. A             | preferred embodiment of the         | invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention            | includes a method for inhibiting | adipocyte differentiation. Highly | preferred indications include       | endocrine disorders (e.g., as | described below under "Endocrine     | Disorders"). Preferred indications | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as     | described below under          | "Hyperproliferative Disorders"),     | blood disorders (e.g., hypertension, | congestive heart failure, blood vessel | blockage, heart disease, stroke, | impotence and/or as described below | under "Immune Activity",         | "Cardiovascular Disorders", and/or    | "Blood-Related Disorders"), immune | disorders (e.g., as described below  | under "Immune Activity"), neural | disorders (e.g., as described below | under "Neural Activity and          | Neurological Diseases"), and | infection (e.g., as described below | under "Infectious Disease"). A | highly preferred indication is | diabetes mellitus. An | additional highly preferred indication | is a complication associated with | diabetes (e.g., diabetic retinopathy, |
| metabolism and cell survival.<br>Exemplary assays for PI3 kinase | activity that may be used or routinely | modified to test PI3 kinase-induced | activity of polypeptides of the | invention (including antibodies and    | agonists or antagonists of the  | invention) include assays disclosed in | Forrer et al., Biol Chem 379(8-  | 9):1101-1110 (1998); Nikoulina et | al., Diabetes 49(2):263-271 (2000); | and Schreyer et al., Diabetes | 48(8):1662-1666 (1999), the contents | of each of which are herein        | incorporated by reference in its   | entirety. Mouse adipocyte cells that | may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary       | mouse adipocyte cells that may be      | used according to these assays   | include 3T3-L1 cells. 3T3-L1 is an  | adherent mouse preadipocyte cell | line that is a continous substrain of | 3T3 fibroblast cells developed     | through clonal isolation and undergo | a pre-adipocyte to adipose-like  | conversion under appropriate        | differentiation conditions known in | the art.                     |                                     |                                |                                |                       |                                        |                                   |                                       |
|                                                                  |                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |
|                                                                  |                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   | _                                     |
|                                                                  |                                        |                                     |                                 |                                        |                                 |                                        |                                  |                                   |                                     |                               |                                      |                                    |                                    |                                      |                                |                                      |                                      |                                        |                                  |                                     |                                  |                                       |                                    |                                      |                                  |                                     |                                     |                              |                                     |                                |                                |                       |                                        |                                   |                                       |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | diabetic nephronathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage (e.g. | due to diabetic neuropathy), blood | vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's | contracture). An additional | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|---------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|-------------------------------------|----------------------------------------|---------------------------------|-----------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                      |                                   |                                        |                                    |                                      |                                      |                                    |                                 |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |
| The state of the s |                                      |                                   |                                        |                                    |                                      |                                      |                                    |                                 |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |

|    |         |     |                         |                                      | Additional highly preferred             |
|----|---------|-----|-------------------------|--------------------------------------|-----------------------------------------|
|    |         |     |                         |                                      | indications are complications           |
|    |         |     |                         |                                      | associated with insulin resistance.     |
|    |         |     |                         |                                      | Additional highly preferred             |
|    |         |     |                         |                                      | indications are disorders of the        |
|    |         |     |                         |                                      | musculoskeletal systems including       |
|    |         |     |                         |                                      | myopathies, muscular dystrophy,         |
|    |         |     |                         |                                      | and/or as described herein.             |
|    |         |     |                         |                                      | Additional highly preferred             |
|    |         |     |                         |                                      | indications include, hypertension,      |
|    |         |     |                         |                                      | coronary artery disease,                |
|    |         |     |                         |                                      | dyslipidemia, gallstones,               |
|    |         |     |                         |                                      | osteoarthritis, degenerative arthritis, |
|    |         |     |                         |                                      | eating disorders, fibrosis, cachexia,   |
|    |         |     |                         |                                      | and kidney diseases or disorders.       |
|    |         |     |                         |                                      | Highly preferred indications include    |
|    |         |     |                         |                                      | neoplasms and cancer, such as,          |
|    |         |     |                         |                                      | lipoma, liposarcoma, lymphoma,          |
|    |         |     |                         |                                      | leukemia and breast, colon, and         |
|    |         |     |                         |                                      | kidney cancer. Additional highly        |
|    |         |     |                         |                                      | preferred indications include           |
|    |         |     |                         |                                      | melanoma, prostate, lung,               |
|    |         |     |                         |                                      | pancreatic, esophageal, stomach,        |
|    |         |     |                         |                                      | brain, liver, and urinary cancer.       |
|    |         |     |                         |                                      | Other preferred indications include     |
|    |         |     |                         |                                      | benign dysproliferative disorders and   |
|    |         |     |                         |                                      | pre-neoplastic conditions, such as,     |
|    |         |     |                         |                                      | for example, hyperplasia, metaplasia,   |
|    |         |     |                         |                                      | and/or dysplasia.                       |
|    | HHFHJ59 | 502 | Production of IL-10 and | Assays for production of IL-10 and   | Highly preferred indications include    |
| 86 |         |     | activation of T-cells.  | activation of T-cells are well known | allergy and asthma. Additional          |
|    |         |     |                         | in the art and may be used or        | highly preferred indications include    |
|    |         |     |                         | routinely modified to assess the     | immune and hematopoietic disorders      |
|    |         |     |                         | ability of polypeptides of the       | (e.g., as described below under         |
|    |         |     |                         | invention (including antibodies and  | "Immune Activity", and "Blood-          |
|    |         |     |                         | agonists or antagonists of the       | Related Disorders"), autoimmune         |
|    |         |     |                         | invention) to stimulate or inhibit   | diseases (e.g., rheumatoid arthritis,   |

|    |         |     |                                                     | production of IL-10 and/or activation and "Cedis. Exemplary assays that may be used or routinely undrifted and unblodies of the invention (robusting and properties) and ambodies of the invention (including angues) or alternative for example, assays such as allowed in causing a fine of the invention of intervention of the invention of the invent | systemic lipus crythemaosis.  Corf.'s desease, multiple sciencis andor sa described below), mumodicinecise (e.g., sa described below), bosting a Tecil mediated immune response, and suppressing a Tecil-mediated immune response. |
|----|---------|-----|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |         |     |                                                     | initiation and pathogenesis of allergy<br>and asthma. Primary Thelper 2<br>cells are generated via in vitro culture<br>under Th2 polarizing conditions<br>using perpletal blood lymphocytes<br>isolated from cord blood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                    |
| 66 | HHGBO91 | 503 | Activation of<br>Adipocyte ERK<br>Signaling Pathway | Kinase assay. Kinase assays, for<br>example an Elk-1 kinase assay, for<br>ERK signal transduction that regulate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly preferred embodiment<br>of the invention includes a method<br>for stimulating adipocyte                                                                                                                                   |

| nroliferation An alternative highly   | preferred embodiment of the          | invention includes a method for      | inhibiting adipocyte proliferation. | A highly preferred embodiment of    | the invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention           | includes a method for inhibiting     | adipocyte differentiation. A      | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below |
|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|---------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|
| cell proliferation or differentiation | are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the  | invention (including antibodies and | agonists or antagonists of the      | invention) to promote or inhibit cell  | proliferation, activation, and  | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      |
|                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |
|                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |
|                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |

| through clonal isolation and undergo | o under "Immune Activity"), neural     |
|--------------------------------------|----------------------------------------|
| a pre-adipocyte to adipose-like      | disorders (e.g., as described below    |
| conversion under appropriate         | under "Neural Activity and             |
| differentiation conditions known in  |                                        |
| the art.                             | infection (e.g., as described below    |
|                                      | under "Infectious Disease").           |
|                                      | ind                                    |
|                                      | diabetes mellitus. An additional       |
|                                      | highly preferred indication is a       |
|                                      | complication associated with           |
|                                      | diabetes (e.g., diabetic retinopathy,  |
|                                      | diabetic nephropathy, kidney disease   |
|                                      | (e.g., renal failure, nephropathy      |
|                                      | and/or other diseases and disorders as |
|                                      | described in the "Renal Disorders"     |
|                                      | section below), diabetic neuropathy,   |
|                                      | nerve disease and nerve damage         |
|                                      | (e.g., due to diabetic neuropathy),    |
|                                      | blood vessel blockage, heart disease,  |
|                                      | stroke, impotence (e.g., due to        |
|                                      | diabetic neuropathy or blood vessel    |
|                                      | blockage), seizures, mental            |
|                                      | confusion, drowsiness, nonketotic      |
|                                      | hyperglycemic-hyperosmolar coma,       |
|                                      | cardiovascular disease (e.g., heart    |
|                                      | disease, atherosclerosis,              |
|                                      | microvascular disease, hypertension,   |
|                                      | stroke, and other diseases and         |
|                                      | disorders as described in the          |
|                                      | "Cardiovascular Disorders" section     |
|                                      | below), dyslipidemia, endocrine        |
|                                      | disorders (as described in the         |
|                                      | "Endocrine Disorders" section          |
|                                      | below), neuropathy, vision             |
|                                      | impairment (e.g., diabetic retinopathy |
|                                      | and blindness), ulcers and impaired    |
|                                      | wound healing, infection (e.g.,        |

| infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly | preferred indications are | complications associated with insulin | resistance. Additional highly | preferred indications are disorders of | the musculoskeletal systems | including myopathies, muscular | dystrophy, and/or as described | herein. Additional highly | preferred indications include, | hypertension, coronary artery | disease, dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, | eating disorders, fibrosis, cachexia, | and kidney diseases or disorders. | Preferred indications include | neoplasms and cancer, such as, | lymphoma, leukemia and breast, | colon, and kidney cancer. Additional | preferred indications include | melanoma, prostate, lung, | pancreatic, esophageal, stomach, | brain, liver, and urinary cancer. | Highly preferred indications include | lipomas and liposarcomas. Other | preferred indications include benign | dysproliferative disorders and pre- |
|--------------------------------------|------------------------------|---------------------------------------|------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------|---------------------------|---------------------------------------|-------------------------------|----------------------------------------|-----------------------------|--------------------------------|--------------------------------|---------------------------|--------------------------------|-------------------------------|------------------------------------|-----------------------------------------|---------------------------------------|-----------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------------|-------------------------------|---------------------------|----------------------------------|-----------------------------------|--------------------------------------|---------------------------------|--------------------------------------|-------------------------------------|
|                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |                                |                           |                                |                               |                                    |                                         |                                       |                                   |                               |                                |                                |                                      |                               |                           |                                  |                                   |                                      |                                 |                                      |                                     |
|                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |                                |                           |                                |                               |                                    |                                         |                                       |                                   |                               |                                |                                |                                      |                               |                           |                                  |                                   |                                      |                                 |                                      |                                     |
|                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |                                |                           |                                |                               |                                    |                                         |                                       |                                   |                               |                                |                                |                                      |                               |                           |                                  |                                   |                                      |                                 |                                      |                                     |

| 100 | 6500001111 | · · |                        |                                                                            | and/or dysplasia.                                       | $\neg$ |
|-----|------------|-----|------------------------|----------------------------------------------------------------------------|---------------------------------------------------------|--------|
|     | HHGCGS3    | 204 | Stimulation of insulin | Assays for measuring secretion of<br>insulin are well-known in the art and | A highly preferred indication is<br>diabetes mellins An |        |
|     |            |     | pancreatic beta cells. | may be used or routinely modified to                                       | additional highly preferred indication                  |        |
|     |            |     |                        | assess the ability of polypeptides of                                      | is a complication associated with                       |        |
|     |            |     |                        | the invention (including antibodies                                        | diabetes (e.g., diabetic retinopathy,                   |        |
|     |            |     |                        | and agonists or antagonists of the                                         | diabetic nephropathy, kidney disease                    |        |
|     |            |     |                        | invention) to stimulate insulin                                            | (e.g., renal failure, nephropathy                       |        |
|     |            |     |                        | secretion. For example, insulin                                            | and/or other diseases and disorders as                  | _      |
|     |            |     |                        | secretion is measured by FMAT                                              | described in the "Renal Disorders"                      |        |
|     |            |     |                        | using anti-rat insulin antibodies.                                         | section below), diabetic neuropathy,                    |        |
|     |            |     |                        | Insulin secretion from panereatic beta                                     | nerve disease and nerve damage                          |        |
|     |            |     |                        | cells is upregulated by glucose and                                        | (e.g., due to diabetic neuropathy),                     |        |
|     |            |     |                        | also by certain proteins/peptides, and                                     | blood vessel blockage, heart disease,                   |        |
|     |            |     |                        | disregulation is a key component in                                        | stroke, impotence (e.g., due to                         |        |
|     |            |     |                        | diabetes. Exemplary assays that may                                        | diabetic neuropathy or blood vessel                     |        |
|     |            |     |                        | be used or routinely modified to test                                      | blockage), seizures, mental                             |        |
|     |            |     |                        | for stimulation of insulin secretion                                       | confusion, drowsiness, nonketotic                       |        |
|     |            |     |                        | (from pancreatic cells) by                                                 | hyperglycemic-hyperosmolar coma,                        |        |
|     |            |     |                        | polypeptides of the invention                                              | cardiovascular disease (e.g., heart                     |        |
|     |            |     |                        | (including antibodies and agonists or                                      | disease, atherosclerosis,                               |        |
|     |            |     |                        | antagonists of the invention) include                                      | microvascular disease, hypertension,                    |        |
|     |            |     |                        | assays disclosed in: Ahren, B., et al.,                                    | stroke, and other diseases and                          |        |
|     |            |     |                        | Am J Physiol, 277(4 Pt 2):R959-66                                          | disorders as described in the                           |        |
|     |            |     |                        | (1999); Li, M., et al., Endocrinology,                                     | "Cardiovascular Disorders" section                      |        |
|     |            |     |                        | 138(9):3735-40 (1997); Kim, K.H.,                                          | below), dyslipidemia, endocrine                         |        |
|     |            |     |                        | et al., FEBS Lett, 377(2):237-9                                            | disorders (as described in the                          |        |
|     |            |     |                        | (1995); and, Miraglia S et. al.,                                           | "Endocrine Disorders" section                           |        |
|     |            |     |                        | Journal of Biomolecular Screening,                                         | below), neuropathy, vision                              |        |
|     |            |     |                        | 4:193-204 (1999), the contents of                                          | impairment (e.g., diabetic retinopathy                  | -      |
|     |            |     |                        | each of which is herein incorporated                                       | and blindness), ulcers and impaired                     |        |
|     |            |     |                        | by reference in its entirety.                                              | wound healing, and infection (e.g.,                     |        |
|     |            |     |                        | Pancreatic cells that may be used                                          | infectious diseases and disorders as                    |        |
|     |            |     |                        | according to these assays are publicly                                     | described in the "Infectious                            |        |
|     |            |     |                        | available (e.g., through the ATCCTM)                                       | Discases" section below, especially                     |        |
|     |            |     |                        | and/or may be routinely generated.                                         | of the urinary tract and skin), carpal                  |        |

|     |         |     |                                                                   | Vermplus punction close list and may be used according to these assays much earl soft and the list. Nest cells are a semi-adherent cell into an A-ray induced rat transplantable and X-ray induced rat transplantable and X-ray induced rat transplantable characteristics typical of mario characteristics typical of mario paracratic bean cells including glucose includible insulia secretion. References: A-Nation c. ab.                                                                                                                                                                                                                                                                                                                                                                             | times syndrome and Dispuyers's contracture). An additional independent of the property of the |
|-----|---------|-----|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 101 | HHGCM76 | 505 | Stimulation of insulin<br>secretion from<br>punceatic beta cells. | Assays for measuring secretion of main are well-washes for the many be used or rounney modified to the invention (including animodies and agonists or animoponists of the invention) to stimulate installin secretion. For example, insulin secretion for example, insulin secretion for example, insulin secretion from parteriors. Insulin secretion from parteriors and animomaly and are insuling and real main anti-holding and real main proteins/perpities, and dishedes. Exemplery seasys in may be used or roundery modified to test for stimulation of insulin secretion (including anti-holding and agoniss or amongoins of the invention) include assays disclosed in: Ahren, E. et al. Endocranology, I., M., et al. Endocranology. | A highly preferred indication is adiabetes mellinas. An additional highly preferred indication is additional highly preferred indication of the complication associated with diabetes (e.g., diabetic refinopathy, didney disease (e.g., renal failure, hephropathy and conditional particles (e.g., the failure, hephropathy, kidney disease (e.g., renal failure, hephropathy and conditional particles and near edianage described in the "Renal Disouters" and cascribed in the "Renal Disouters" and cascribed in the "Renal Disouters and near edianage of each the olderige, heard disease, near disease, and near disease, and near disease, and or crossing or blood vessel blockage, heard disease, importence (e.g. due to dischict neuropathy or blood vessel blockage) sciences, morned countries of constitues, to morned or hypergly-commic-typerconstroller countries, and offer diseases as undered as descenced, hyperglasses, hyperconstroller in the diseases, and conditions of the diseases and conditions are study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| HHGCM6 | 505 | Production of JCAM-1 | et al. HBMs Lett, 37(12):231-9<br>(1995); and, Miraginia S.c. al.,<br>A:192-204 (1999), the contents of<br>command of Biomedicantia Screening,<br>4:192-204 (1999), the contents of<br>by reference in its entirety.<br>Demonstrate of the standard of the standard<br>according to these usasys are publicly<br>according to these usasys are publicly<br>according to these usasys are publicly<br>according to these usasys are<br>according to these usasys<br>and the standard transplantable<br>include rat INS-1 cells. INS-1 cells.<br>Exemplary panceasic cells that may<br>be used according to these assays<br>include rat INS-1 cells. INS-1 cells.<br>Exemplary panceasic cells that may<br>be tased according to these assays<br>include and TNS-1 cells. TNS-1 cells.<br>The propose of the propose of the propose of the single of maintee<br>panceatic beat cells including<br>panceatic short and according<br>Assays for measuring expression of<br>Assays for measuring expression of<br>and may be used or onlinely.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | reflectives (se described in the Pistodorine Disordors' section in the productive of the development of the productive of the urinary tract and skin), carput tunnel syndrome and Dapaytera's of the urinary tract and skin), carput tunnel syndrome and Dapaytera's highly preferred indication is obesity. Additional highly preferred indication is obesity, Additional highly preferred indications is operated with obesity. Additional highly preferred indications is operated with obesity. Additional highly preferred indications are complications associated with installin resistance.  Preferred embodiments of the invention for antipolicy, and productive of the invention for antipolicy. |
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|        |     |                      | modified to assess the ability of populous modified to assess the ability of populous of the invention of including analocides and agonists or analocides and agonists or egalate (CAM-1 expression modified to measure (CAM-1 expression modified to says a continely modified to measure (CAM-1 expression modified usays and (CAM-1 expression modified usays and (CAM-1 expression modified usays and (CAM-1 expression modified and (CAM-1 expression modified to make a continely modified to modified to a continely modified to a cont | with Thereton (value and another agentists, or analgonists thereton, algorists, prevention, and ceretonist algorists, prevention, and/or treatment of Inflammation, Vascular Disease, Athereoscierosis, Resterosis, and Stroke                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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|                                                                                                                                                                                                                                                                                                                                                                                                         | A highly perferred embediment of the invention includes a method for scinning adiptocyte for scinning adiptocyte proliferation. An alternative highly preferred embediment of the invention includes a method for inhibiting adipcyte proliferation. A highly preferred embediment of the invention includes a method for inhibiting adipcyte proliferation. A highly preferred embediment of the invention includes a method for adipcyce differentiation. A display preferred embediment of the invention includes a method for adipcyce differentiation. A highly preferred embediment of the adipcyce distributing (e.g., increasing) addipcyces distribution. A highly preferred embediment of the adipcyce distribution and adipcyces. In invention in adipcyce distribution of (e.g., increasing) addipcyces. Illighly preferred embediment of the decreasing and invention in indications indications include endocrine indications and indications include endocrine indications are indications increasing indications increasing indications increasing indications |
| contents of each of which is breein in surpoyned by televence in its entirely. Cells that may be used enought of better assers are publicly available (e.g., through the ATC/TV) available (e.g., through the ATC/TV). Exemplary cells that may be used andor may be nothinely generated. Exemplary cells that may be used according to these assays include according to these assays include (MAYEC). | ceample an Elei Kinase sassy, for<br>the Res spart Intendention that regulate<br>cell pondification or differentiation<br>to pondification or differentiation<br>or differentiation or differentiation<br>to differentiation or differentiation<br>are well known in the art and may be<br>used or routinely modified to assess<br>invention (including authorities and<br>agonists or amagonists or the<br>agonists or amagonists or the<br>proliferentiation. Exemplary sassys for<br>general control of the properties of the<br>proliferentiation. Exemplary sassys for<br>ERK kinese activity data may be used<br>ERK kinese activity data may be used<br>ERK kinese activity data may be used<br>ERK kinese activity data may be used<br>for extunitely modified to use IERK<br>kinese-included activity of<br>Kinese-included activity of<br>Containing modified to use IERK<br>kinese-included activity of<br>the measure of the invention include<br>the assay of activity of<br>1095), Le Marchand-Brussel Y. Exp.<br>(1998), Le Marchand-Brussel (1999),<br>(2001), and (2011), and (2048)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                         | Activation of Addivocyte ERK Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                         | 909                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                         | HHGC034                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                         | 102                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hypeproliferative Disorders"). | rreterred materiors include blood lisouders (e.g., hypertension, congestive heart failure, blood vessel olockage, heart disease, stroke, mimotence and/or as described below inder "Immune Activity." Cardiovascular Disouders", and/or | "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and inferion (e.g. as described below neurological Diseases"), and | and "Theritous Disease")  A highly proferred indication is a faithful and indication is a faithful and proper and indication is a solid properted indication is a solid properted indication is a solid properted indication is a faithful associated with the complication associated with disease (e.g., disease (e.g., disease), kidney diseases and diseases. | described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g. due to disbetto eneuropathy), blood vessel blockage, hear disease, seruke, impotence (e.g., due to disbetto eneuropathy or blood vessel blockage), seruke, impotence (e.g., due to bloodsage), seiz/nes, mental blockage), seiz/nes, mental seiz/n |
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| of<br>that                                                                                                                | may be used accounting to mese assays are publicly available (e.g., farming the ATCCTM). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-LL cells. 3T3-LL is an addrerent mouse preadpocyte cell | line that is a continuous substrain of 313 fibooblast cells developed through clonal isolation and undergo a pre-adiposyte to adipose-like conversion under appropriate differentiation conditions known in 11th and                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly | preferred indications are | complications associated with insulin | resistance. Additional highly | preferred indications are disorders of | the musculoskeletal systems | including myopathies, muscular | × | herein. Additional highly | preferred indications include, | hypertension, coronary artery | disease, dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, | eating disorders, fibrosis, cachexia, |
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| Preferred indications include anoplasms and caneer, such as, lymphoma, lenkenia and benest, colon, and kidnoul persent didications include medianoma, prostate, lung mancanic, colong and colong and colong and colong and colong and colong and persent didications include medianoma, prostate, lung hordered indications include lipomus and liposucomas. Other preferred indications include benign deprolification (searches and pre-noplastic conditions, such as, for example, hyperplassis, meraplassis, meraplassis, and expensional programments. | A highly preferred indication is diabetes mellinas. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, blancy disease (e.g., retal failure, replinopathy and work on the diseases and diseaders as described in the 'Renal Diseases and mange (e.g., due to diabetic neuropathy). Blood vessel blockege, heart disease, service, importere (e.g., due to diabetic neuropathy) or blood vessel blockege, heart disease, stroke, importere (e.g., due to diabetic neuropathy) or blood vessel blockege), sezures, mernil blockege), sezures, mernil blockege), sezures, mernil disease, controvascular disease, controvascular disease, disperentation, disease, hyperetation, desires, hyperetation, desires, hyperetation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | stassys for measuring existing that are well-known in the art and may be mirror for furthering antibodies and invention (trubuling antibodies and propositions or angular department of the propositions or angular department of the more than the art of th |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Strimutaton of Calcium<br>Flux in puncreatic bea<br>cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|     |         |     |                                                                  | assays disclosed in: Satin LS, et al.,<br>Theorimology, 16(10),4589-601.<br>(1995),240-602.<br>Endocrimology, 15(40),2458-601.<br>Endocrimology, 15(40),2458-601.<br>Endocrimology, 15(40),2459-60.<br>Endocrimology, 15(40),249-60.<br>Endocrimology, 15(40),249-60.<br>Endocrimology, 15(40),249-60.<br>Endocrimology, 15(40),249-60.<br>Endocrimology, 15(40),249-60.<br>Endocrimology, 15(40),249-60.<br>Endocrimology, 16(40),249-60.<br>Endocrimology, 16(40),249-60. | "Cucliovascialar Disorders' section for clariovascialar Disorders' section disorders as described in the disorders' described in the disorders' described in the Tiradocrine Disorders' section below), neuropathy, vision impairment (e.g., disterior retinopathy and bindress), luckes and impaired wound healing, and infection (e.g., microtons diseases and disorders is described in the "Infections as and Dispuyers' sommet syndrome and Dispuyers' sommet syndrome and Dispuyers' sommet syndrome and Dispuyers' sommet when the preferred many preferred many preferred mander or emplications is secarated with obesity. Additional Ingish preferred alternatively, weight gain.  The dispuyers of the preferred alternatively, weight gain.  The dispuyer are complications associated with insulin resistance. |
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| 103 | HHPEN62 | 507 | Proliferation of pre-<br>adipose cells (such as<br>3T3-L1 cells) | Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| invention (including antibodies and arguests or antigonists of the group or gradue viabelity and programs of the confiltration of pead-allowse cells and cell lines. For example, the runninescent Cell Tell-Tecl-Gold Luminescent Cell Vishility Assay (Promega Corp., Madison, W. U.S.A.) can be used to measure the number of vishe cells in culture based on quantitation of the pressure of metabolically active presence of metabolically active presented for standards of the pressure of the chololically active cell line. It is a mouse preadproyer cell line. It is a mouse preadproyer cell line. It is a mouse preadproyer cell ine. It is a cloud is standard of the choral salation. Cells were cloud isolation. Cells were breath and prose-like state before their guest in the succen. See Chern H and Menth M., Cell 3: 127-133 (1974), which is herein in its entirety. | The reporter says measures activation or the NRB signaling pathway in Ku81.2 human baspoili cell line. Assays for the activation or thinking of the activation or mibilition of the activation or mibilition of measuription thought the VRR13 responses clement are well-known in modified to assess he achility of polypeptides of the invention of polypeptides of the invention of polypeptides of the invention of antiquing amplication and against a present of the invention of authorities and against NRB and antipulation of the invention in activation factors and modified capression of a measuriprior factors and modified expression of |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Vertication or inhibition of transcription through NFR3 response cleared in immune cells (each as besophils).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 507                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HHPEN62                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| immunonodulatory genes. NFKB is | important in the pathogenesis of | asthma. Exemplary assays for | transcription through the NFKB | response element that may be used or | rountinely modified to test NFKB- | response element activity of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assavs disclosed in Berger et al | Gene 66:1-10 (1998): Cullen and | Malm Methods in Enzymol | 216:362-368 (1992): Henthorn et al | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Marone et al, Int Arch | Allergy Immunol 114(3):207-17 | (1997), the contents of each of which | are herein incorporated by reference | in its entirety. Cells were pretreated | with SID supernatants or controls for | 15-18 hours, and then 10 ng/mL of | TNF was added to stimulate the | NFkB reporter. SEAP activity was | measured after 48 hours. Basophils | that may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary | human basophil cell lines that may be | used according to these assays | include Ku812, originally established | from a patient with chronic | myelogenous leukemia. It is an | immature prebasophilic cell line that | can be induced to differentiate into | mature basophils. See, Kishi et al., | Leuk Res. 9:381-390 (1985); Blom et |
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| al., Eur J Immunol. 22:2025-32 (1992), where the contents of each are herein incorporated by reference in its entirety. | regulatory Assay; construct contains<br>regulatory and coding sequence of<br>gashere; synthesis, the first specific<br>enzyme in the cholesterol test specific<br>enzyme in the cholesterol test specific<br>enzyme in the cholesterol test specific<br>at 1. 13 Hot. Chem 268:1281; 1<br>128-241(99); the contents of which<br>in its entirety, Cells were treated<br>in its entirety, Cells were treated<br>in the children of the content of<br>activity was measured after 72 hours<br>enversionan ed. Il me (AVICC <sup>o</sup> HB-<br>corrinoma ed.) Il net (AVICC <sup>o</sup> HB-<br>corrinoma ed.) Into the contents of<br>209-497-9 (1980), the contents of<br>reference in its entirety. | stayes for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including anthodies new adomston entagonists of the invention) to simulate insulin secretion. For example, insulin secretion for semantle, insulin secretion from panceaic better the is inspegalated by glucose and disregulation is a key component in disregulation is a key component in disregulation is a key component in behaves. Exemples seaso, it at may be used or routinely modified to test                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                         | synthesis of squarec<br>synthesis gene<br>trenstription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|                                                                                                                         | ИАВВ94                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | НАВВ94                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                         | 104                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 104                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| TOT SUITIBLIANDED OF THIS MINISTERIOR  | comusion, drowsmess, nonkerone         |
|----------------------------------------|----------------------------------------|
| (from pancreatic cells) by             | hyperglycemic-hyperosmolar coma,       |
| polypeptides of the invention          | cardiovascular disease (e.g., heart    |
| (including antibodies and agonists or  | disease, atherosclerosis,              |
| antagonists of the invention) include  | microvascular disease, hypertension,   |
| assays disclosed in: Shimizu, H., et   | stroke, and other diseases and         |
| al., Endocr J, 47(3):261-9 (2000);     | disorders as described in the          |
| Salapatck, A.M., et al., Mol           | "Cardiovascular Disorders" section     |
| Endocrinol, 13(8):1305-17 (1999);      | below), dyslipidemia, endocrine        |
| Filipsson, K., et al., Ann N Y Acad    | disorders (as described in the         |
| Sci, 865:441-4 (1998); Olson, L.K.,    | "Endocrine Disorders" section          |
| et al., J Biol Chem, 271(28):16544-    | below), neuropathy, vision             |
| 52 (1996); and, Miraglia S et. al.,    | impairment (e.g., diabetic retinopathy |
| Journal of Biomolecular Screening,     | and blindness), ulcers and impaired    |
| 4:193-204 (1999), the contents of      | wound healing, and infection (e.g.,    |
| each of which is herein incorporated   | infectious diseases and disorders as   |
| by reference in its entirety.          | described in the "Infectious           |
| Pancreatic cells that may be used      | Diseases" section below, especially    |
| according to these assays are publicly | of the urinary tract and skin), carpal |
| available (e.g., through the ATCCTM)   | tunnel syndrome and Dupuytren's        |
| and/or may be routinely generated.     | contracture). An additional            |
| Exemplary pancreatic cells that may    | highly preferred indication is obesity |
| be used according to these assays      | and/or complications associated with   |
| include HITT15 Cells. HITT15 are       | obesity. Additional highly preferred   |
| an adherent epithelial cell line       | indications include weight loss or     |
| established from Syrian hamster islet  | alternatively, weight gain. Additional |
| cells transformed with SV40. These     | highly preferred indications are       |
| cells express glucagon, somatostatin,  | complications associated with insulin  |
| and glucocorticoid receptors. The      | resistance.                            |
| cells secrete insulin, which is        |                                        |
| stimulated by glucose and glucagon     |                                        |
| and suppressed by somatostatin or      |                                        |
| glucocorticoids. ATTC# CRL-1777        |                                        |
| Refs: Lord and Ashcroft. Biochem.      |                                        |
| J. 219: 547-551; Santerre et al. Proc. |                                        |
| Natl. Acad. Sci. USA 78: 4339-4343,    |                                        |
| 1981.                                  |                                        |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An allerantwo preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications.             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Assays for the regulation (Leteroresses of exclusion) the creates of exclusions of cells in vitro are used or realized or of cells in vitro are used or realized to of cells in vitro are used or realized to modified to assess the ability of polyperdies of the invention (including antibodies and invention) (including antibodies and invention) to regulate viability and invention) to regulate viability and invention to regulate viability and cell lines. For example, the CellTitter-folio Imminescent Cell CellTitter-folio Imminescent Cell CellTitter-folio Imminescent Cell Madisam, WI, USA) can be used to cell lines. For example, the CellTitter-folio Imminescent Cell inclusion of the CellTitter-folio Imminescent Cell inclusion and the pressure of metabolically active of the pressure of metabolically active pressure of metabolically active clear Hand Menth M., Cell 3 127-131 (1974), which is herein in seminery. | Assays for the activation of<br>maceriphon though the Semm<br>Response Element (SRE) are well-<br>stown in the art and may be used or<br>routinely modified to assess the<br>ability of polypeptides of the<br>invention (including antibodies and<br>against or anagoniss of the |
| Politention of pre- adpose cells (such as 313-L1 cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Activation of transcription through serum response element in immune cells (such as T-cells).                                                                                                                                                                                     |
| 609                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 510                                                                                                                                                                                                                                                                               |
| HJACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HJACG30                                                                                                                                                                                                                                                                           |
| 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 106                                                                                                                                                                                                                                                                               |

| invention) to regulate the serum        | include blood disorders (e.g., as      |
|-----------------------------------------|----------------------------------------|
| expression of genes involved in         | Activity", "Blood-Related              |
| growth. Exemplary assays for            | Disorders", and/or "Cardiovascular     |
| transcription through the SRE that      | Disorders"), Highly preferred          |
| may be used or routinely modified to    | indications include autoimmune         |
| test SRE activity of the polypeptides   | diseases (e.g., rheumatoid arthritis,  |
| of the invention (including antibodies  | systemic lupus crythematosis,          |
| and agonists or antagonists of the      | Crohn"s disease, multiple sclerosis    |
| invention) include assays disclosed in  | and/or as described below),            |
| Berger et al., Gene 66:1-10 (1998);     | immunodenciencies (e.g., as            |
| Enzymol 216:362-368 (1992):             | mediated immine response and           |
| Henthorn et al., Proc Natl Acad Sci     | suppressing a T cell-mediated          |
| USA 85:6342-6346 (1988); and            | immune response. Additional highly     |
| Black et al., Virus Genes 12(2):105-    | preferred indications include          |
| 117 (1997), the content of each of      | inflammation and inflammatory          |
| which are herein incorporated by        | disorders, and treating joint damage   |
| reference in its entirety. T cells that | in patients with rheumatoid arthritis. |
| may be used according to these          | An additional highly preferred         |
| assays are publicly available (e.g.,    | indication is sepsis. Highly           |
| through the ATCCTM). Exemplary          | preferred indications include          |
| mouse T cells that may be used          | neoplastic diseases (e.g., leukemia,   |
| according to these assays include the   | lymphoma, and/or as described          |
| CTLL cell line, which is an IL-2        | below under "Hyperproliferative        |
| dependent suspension culture of T       | Disorders"). Additionally, highly      |
| cells with cytotoxic activity.          | preferred indications include          |
|                                         | neoplasms and cancers, such as, for    |
|                                         | example, leukemia, lymphoma,           |
|                                         | melanoma, glioma (e.g., malignant      |
|                                         | glioma), solid tumors, and prostate,   |
|                                         | breast, lung, colon, pancreatic,       |
|                                         | esophageal, stomach, brain, liver and  |
|                                         | urinary cancer. Other preferred        |
|                                         | indications include benign             |
|                                         | dysproliferative disorders and pre-    |
|                                         | neoplastic conditions, such as, for    |

| example, hyperplasia, metaplasia, motoplasia, moto dysplasia. Preferred indications include anemia, hyperplasia include anemia, through a propoperia, ledeglin's factoria include anemia, through a propoperia, ledeglin's factoria include a propoperia, ledglin's factoria includenta, propoperia, ledglin's factoria includenta, propoperia, ledglin's factoria includenta, proposasion of immune reactions to immune reactions to arraylanch of operas and itsus, herrophila, hyperoagulation, disease, influences mellines, enchoarditis, memigiis, Lyme Disease, cardiae memigiis, Lyme Disease, cardiae memigiis, lyme Disease, cardiae memigiis, lyme Disease, cardiae metaplasis infection (e.g., an allegion in infection (e.g., an indication is infection (e.g., an indication is infection (e.g., an indication is infection (e.g., an indication) is successful. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | regulatory and ooding sequence of squalette synthesase, the first specific sequence of squalette synthesase, the first specific sequence in strong in the following sequence of biosynthesic pathway. See Jang, et al. 1810. Chem. 26812818.  128241(95), the counterns of which with SID supernatura, and SEAP activity was unestand fair PT 2 hours. Hep62 is a human hepatochlata excitoriate edit in the cA frow Hep See Sections and Hind (A TCV HB-8065). See Knowless et al., Science. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | synthetics of squalene<br>transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HIACG30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 106                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|     |         |     |                        | reference in its entirety.              |                                        |
|-----|---------|-----|------------------------|-----------------------------------------|----------------------------------------|
|     | HJACG30 | 510 | Stimulation of insulin | Assays for measuring secretion of       | A highly preferred indication is       |
| 901 |         |     | secretion from         | insulin are well-known in the art and   | diabetes mellitus. An                  |
|     |         |     | pancreatic beta cells. | may be used or routinely modified to    | additional highly preferred indication |
|     |         |     |                        | assess the ability of polypeptides of   | is a complication associated with      |
|     |         |     |                        | the invention (including antibodies     | diabetes (e.g., diabetic retinopathy,  |
|     |         |     |                        | and agonists or antagonists of the      | diabetic nephropathy, kidney disease   |
|     |         |     |                        | invention) to stimulate insulin         | (e.g., renal failure, nephropathy      |
|     |         |     |                        | secretion. For example, insulin         | and/or other diseases and disorders as |
|     |         |     |                        | secretion is measured by FMAT           | described in the "Renal Disorders"     |
|     |         |     |                        | using anti-rat insulin antibodies.      | section below), diabetic neuropathy,   |
|     |         |     |                        | Insulin secretion from pancreatic beta  | nerve disease and nerve damage         |
|     |         |     |                        | cells is upregulated by glucose and     | (e.g., due to diabetic neuropathy),    |
|     |         |     |                        | also by certain proteins/peptides, and  | blood vessel blockage, heart disease,  |
|     |         |     |                        | disregulation is a key component in     | stroke, impotence (e.g., due to        |
|     |         |     |                        | diabetes. Exemplary assays that may     | diabetic neuropathy or blood vessel    |
|     |         |     |                        | be used or routinely modified to test   | blockage), seizures, mental            |
|     |         |     |                        | for stimulation of insulin secretion    | confusion, drowsiness, nonketotic      |
|     |         |     |                        | (from pancreatic cells) by              | hyperglycemic-hyperosmolar coma,       |
|     |         |     |                        | polypeptides of the invention           | cardiovascular disease (e.g., heart    |
|     |         |     |                        | (including antibodies and agonists or   | disease, atherosclerosis,              |
|     |         |     |                        | antagonists of the invention) include   | microvascular disease, hypertension,   |
|     |         |     |                        | assays disclosed in: Ahren, B., et al., | stroke, and other diseases and         |
|     |         |     |                        | Am J Physiol, 277(4 Pt 2):R959-66       | disorders as described in the          |
|     |         |     |                        | (1999); Li, M., et al., Endocrinology,  | "Cardiovascular Disorders" section     |
|     |         |     |                        | 138(9):3735-40 (1997); Kim, K.H.,       | below), dyslipidemia, endocrine        |
|     |         |     |                        | et al., FEBS Lett, 377(2):237-9         | disorders (as described in the         |
|     |         |     |                        | (1995); and, Miraglia S et. al.,        | "Endocrine Disorders" section          |
|     |         |     |                        | Journal of Biomolecular Screening,      | below), neuropathy, vision             |
|     |         |     |                        | 4:193-204 (1999), the contents of       | impairment (e.g., diabetic retinopathy |
|     |         |     |                        | each of which is herein incorporated    | and blindness), ulcers and impaired    |
|     |         |     |                        | by reference in its entirety.           | wound healing, and infection (e.g.,    |
|     |         |     |                        | Pancreatic cells that may be used       | infectious diseases and disorders as   |
|     |         |     |                        | according to these assays are publicly  | described in the "Infectious           |
|     |         |     |                        | available (e.g., through the ATCCTM)    | Discases" section below, especially    |
|     |         |     |                        | and/or may be routinely generated.      | of the urinary tract and skin), carpal |
|     |         |     |                        | Exemplary pancreatic cells that may     | tunnel syndrome and Dupuytren's        |

| s inchestration of a registration of the state of the state of complications associated with norm debesty. Additional highly preferred he indications include weight uses of the state of t | we display proferred indication is a complexes near thickness of the property  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| he used according to these assays include an INS1 cells are a semi-adherent cell line an X-ray indirect for timesplantable insultinoma. These cells reading characteristics typical of matric characteristics typical of matric paracteristics typical of matric paracteristics and paracteristics and paracteristics and in matric gluoses riducible insultin secretical fallows. Ballows individual according gluoses riducible insultin secretical individual and individual according a paracteristics. Assist et al. Endocranology 1992; 1991; 67.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Assays for the regulation of viability and politication of cells, in vitro are cells.  In well-known in the art and may be used or rouningly modified to issess the ability of polypeptides of the invention (including authorities and agonists or antegonists of the invention) to pancratic of the rouningly to polypeptides of the invention of pancratic beta cells.  For example, the Cell Tire-cilo huminescent cell viability assay measures the murber of viability and polification of pancratic beta cells.  For example, the Cell Tire-cilo huminescent cell viability assay in culture based on quantitation of humenscent which against the presence of including author of the presence of retarbolically active colls. Exemplation of viability and regulation of pancratic beat cells by polypeptides of the invention (including authorities and possible of the invention) including and magonisis of the invention of managonisis of the managonis of the invention of managonis of the managonis of the managonis of the managonis of the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | S11 Regulation of viability and politication of pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 107 IMBC/35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| agonists or antagonists of the               | cell proliferation is inhibited. A      |
|----------------------------------------------|-----------------------------------------|
| invention) include assays disclosed in       | preferred embodiment of the             |
| Forrer et al., Biol Chem 379(8-              | invention includes a method for         |
| 9):1101-1110 (1998); Nikoulina et            | stimulating muscle cell                 |
| al., Diabetes 49(2):263-271 (2000);          | differentiation. In a specific          |
| and Schreyer et al., Diabetes                | embodiment, skeletal muscle cell        |
| 48(8):1662-1666 (1999), the contents         | differentiation is stimulated. An       |
| of each of which are herein                  | alternative highly preferred            |
| incorporated by reference in its             | embodiment of the invention             |
| entirety. Rat myoblast cells that may        | includes a method for inhibiting        |
| be used according to these assays are        | muscle cell differentiation. In a       |
| publicly available (e.g., through the        | specific embodiment, skeletal muscle    |
| ATCC <sup>TM</sup> ). Exemplary rat myoblast | cell differentiation is inhibited.      |
| cells that may be used according to          | Highly preferred indications include    |
| these assays include L6 cells. L6 is         | disorders of the musculoskeletal        |
| an adherent rat myoblast cell line,          | system. Preferred indications           |
| isolated from primary cultures of rat        | include neoplastic diseases (e.g., as   |
| thigh muscle, that fuses to form             | described below under                   |
| multinucleated myotubes and striated         | "Hyperproliferative Disorders"),        |
| fibers after culture in differentiation      | endocrine disorders (e.g., as           |
| media.                                       | described below under "Endocrine        |
|                                              | Disorders"), neural disorders (e.g., as |
|                                              | described below under "Neural           |
|                                              | Activity and Neurological               |
|                                              | Diseases"), blood disorders (e.g., as   |
|                                              | described below under "Immune           |
|                                              | Activity", "Cardiovascular              |
|                                              | Disorders", and/or "Blood-Related       |
|                                              | Disorders"), immune disorders (e.g.,    |
|                                              | as described below under "Immune        |
|                                              | Activity"), and infection (e.g., as     |
|                                              | elov                                    |
|                                              | Disease"). A highly preferred           |
|                                              | indication is diabetes mellitus.        |
|                                              | An additional highly preferred          |
|                                              | indication is a complication            |
|                                              | associated with diabetes (e.g.,         |

|  |  | diahetic retinonathy diahetic          |
|--|--|----------------------------------------|
|  |  | manora remobanty, manora               |
|  |  | nephropathy, kidney disease (e.g.,     |
|  |  | renal failure, nephropathy and/or      |
|  |  | other diseases and disorders as        |
|  |  | described in the "Renal Disorders"     |
|  |  | section below), diabetic neuropathy,   |
|  |  | nerve disease and nerve damage (e.g,   |
|  |  | due to diabetic neuropathy), blood     |
|  |  | vessel blockage, heart disease,        |
|  |  | stroke, impotence (e.g., due to        |
|  |  | diabetic neuropathy or blood vessel    |
|  |  | blockage), seizures, mental            |
|  |  | confusion, drowsiness, nonketotic      |
|  |  | hyperglycemic-hyperosmolar coma,       |
|  |  | cardiovascular disease (e.g., heart    |
|  |  | disease, atherosclerosis,              |
|  |  | microvascular disease, hypertension,   |
|  |  | stroke, and other diseases and         |
|  |  | disorders as described in the          |
|  |  | "Cardiovascular Disorders" section     |
|  |  | below), dyslipidemia, endocrine        |
|  |  | disorders (as described in the         |
|  |  | "Endocrine Disorders" section          |
|  |  | below), neuropathy, vision             |
|  |  | impairment (e.g., diabetic retinopathy |
|  |  | and blindness), ulcers and impaired    |
|  |  | wound healing, infections (e.g.,       |
|  |  | infectious diseases and disorders as   |
|  |  | described in the "Infectious           |
|  |  | Diseases" section below, especially    |
|  |  | of the urinary tract and skin), carpal |
|  |  | tunnel syndrome and Dupuytren's        |
|  |  | contracture). An additional            |
|  |  | highly preferred indication is obesity |
|  |  | and/or complications associated with   |
|  |  | obesity. Additional highly preferred   |
|  |  | indications include weight loss or     |

|     |         |     |                      |                                          | alternatively, weight gain. Additional highly preferred indications are complications |
|-----|---------|-----|----------------------|------------------------------------------|---------------------------------------------------------------------------------------|
|     |         |     |                      |                                          | associated with insulin resistance.<br>Additional highly preferred                    |
|     |         |     |                      |                                          | indications are disorders of the<br>musculoskeletal system including                  |
|     |         |     |                      |                                          | myopathics, muscular dystrophy,                                                       |
|     |         |     |                      |                                          | and/or as described herein.<br>Additional highly preferred                            |
|     |         |     |                      |                                          | indications include: myopathy,                                                        |
|     |         |     |                      |                                          | atrophy, congestive heart failure,<br>cachexia myxomas fibromas                       |
|     |         |     |                      |                                          | congenital cardiovascular                                                             |
|     |         |     |                      |                                          | abnormalities, heart disease, cardiac                                                 |
|     |         |     |                      |                                          |                                                                                       |
|     |         |     |                      |                                          | vascular disease. Highly                                                              |
|     |         |     |                      |                                          | preferred indications include                                                         |
|     |         |     |                      |                                          | neoplasms and cancer, such as,                                                        |
|     |         |     |                      |                                          | rhabdomyoma, rhabdosarcoma,                                                           |
|     |         |     |                      |                                          | stomach, esophageal, prostate, and                                                    |
|     |         |     |                      |                                          | urnary cancer. Preferred indications                                                  |
|     |         |     |                      |                                          | also include breast, lung, colon,                                                     |
|     |         |     |                      |                                          | pancreatic, brain, and liver cancer.                                                  |
|     |         |     |                      |                                          | Other preferred indications include                                                   |
|     |         |     |                      |                                          | benign dysproliterative disorders and                                                 |
|     |         |     |                      |                                          | pre-ncopiasue conditions, such as,                                                    |
|     |         |     |                      |                                          | nyperpiasia, metapiasia, and or<br>dysplasia.                                         |
|     | HJPAD75 | 512 | Activation of T-Cell | Kinase assay. JNK and p38 kinase         | Preferred indications include                                                         |
| 108 |         |     | p38 or JNK Signaling | assays for signal transduction that      | neoplastic diseases (e.g., as described                                               |
|     |         |     | Pathway.             | regulate cell proliferation, activation, | below under "Hyperproliferative                                                       |
|     |         |     |                      | or apoptosis are well known in the art   | Disorders"), blood disorders (e.g., as                                                |
|     |         |     |                      | and may be used or routinely             | described below under "Immune                                                         |
|     |         |     |                      | modified to assess the ability of        | Activity", "Cardiovascular                                                            |
|     |         |     |                      | polypeptides of the invention            | Disorders", and/or "Blood-Related                                                     |
|     |         |     |                      | (including antibodies and agonists or    | Disorders"), and infection (e.g., an                                                  |

| antagonists of the invention) to promote or inflor innume cell (e.g. Treath) ponification, activation, and apoposas. Exemplary assays for NK and p.38 kinase activity that may be used or roundary modeled to test of the invention) of the person of the invention of including antibodies and agenists or probypeptides of the invention) include the assays disclosed in Forner et al. Bibl Chean 376(9.94); 101–110 (1998); Gupta et al. Bibl Chean 376(9.94); 101–110 (1998); Gupta et al. Bibl Chean 376(9.94); Included the assays disclosed in Forner et al. Bibl Chean 376(9.94); Included the assays disclosed in Forner et al. Bibl Chean 376(9.94); Included the assays disclosed in Forner et al. Bibl Chean 376(9.94); Included the assays with the antibodies and Karin, Maure (1998); Gupta et al. Bibl T(J.) 4370-500 (1999); the contents of et al. Exp. (1999); Chang and Karin, Maure (1998); Chang and Ary (1998); Chang and Karin, Maure (1998); Chang and Ary (1998 | managonists of the inventional) to promise or rinkful immune ed Treell) profileration, activation, and proposed is Everphylay assays 14 M. and p.8 kinase activity in the assays disclosed in Forent Biol Chem 7378(s.y.) [101-118]  M. Biochem See, Stymp 64:29, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174-170, 174 | $\vdash$                         | 1 (e.g.   under "Infectious Disease"). Highly | , and preferred indications include | or autoimmune diseases (e.g.,   | at may   rheumatoid arthritis, systemic lupus | o test erythematosis, multiple sclerosis | _                                   | n immunodeficiencies (e.g., as   | -                              | clude preferred indications include | et al., inflammation and inflammatory | disorders. Highly preferred  |                                    | kis diseases (e.g., leukemia, lymphoma, |                               | Ė                               | Obb Highly preferred indications include | _                               |                                    | breast, lung, colon, pancreatic, | Ť                                | _                                | _                                      | _                            | _                                       | these example, hyperplasia, metaplasia, | ne, and/or dysplasia. Preferred |                            | h AIDS, allergy, anemia, pancytopenia, | leukopenia, thrombocytopenia, | Hodgkin"s disease, acute | lymphocytic anemia (ALL), | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, granulomatous | disease, inflammatory bowel disease, | sepsis, psoriasis, suppression of |  |
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-------------------------------------|-----------------------------------------|---------------------------------|----------------------------|----------------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------------|-----------------------------------|--------------------------------------|-----------------------------------|--|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | antagonists of the invention) to | promote or inhibit immune cell                | T-cell) proliferation, activation   | apoptosis. Exemplary assays for | JNK and p38 kinase activity that may          | be used or routinely modified to test    | JNK and p38 kinase-induced activity | of polypeptides of the invention | (including antibodies and agon | antagonists of the invention) in    | the assays disclosed in Forrer e      | Biol Chem 379(8-9):1101-1110 | (1998); Gupta et al., Exp Cell Res | 247(2): 495-504 (1999); Kyrial          | JM, Biochem Soc Symp 64:29-48 | (1999); Chang and Karin, Nature | 410(6824):37-40 (2001); and Cobb         | MH, Prog Biophys Mol Biol 71(3- | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. T cells that may be us | according to these assays are publicly | available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary mouse ' | that may be used according to these     | assays include the CTLL cell li | which is an IL-2 dependent | suspension-culture cell line with      | cytotoxic activity.           |                          |                           |                                  |                                   |                                      |                                   |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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                                |                                         |                                 |                            |                                        |                               |                          |                           |                                  |                                   |                                      |                                   |  |

| organs and tissues, endocarditis, meningitis, and Lyme Disease. | the invention includes a method for mandating (e.g., increasing) LL-6 production. An alternative lightly producted method for mindrating (e.g., increasing) LL-6 production. An alternative lightly producted condendment of the invention includes a method for invention includes a method for invention includes a method for condenders of highly profured include in the production. A highly predicted indications is include blood disorders (e.g. as described blood disorders (e.g. as described blood disorders (e.g. as described blood disorders (e.g., as described blood disorders). And for "Cardiovascular Disorders"), and for "Cardiovascular Disorders"). And winder "Infections Disease"). Highly predicted discinations is include between diseases (e.g., and the mindred fields in the predicted discinations is include bosting as a secretable delow). Highly preferred infinite responses and alternatively suppressing a B cell-mindrations also include bosting as B cell-midited immune responses Highly preferred discinations is include sometime includes saftma and inflammanory disorders. Additional highly preferred indications include saftma and inflammanory disorders Additional highly preferred indications include saftma and inflammanory disorders. Additional highly preferred indications include saftma and inflammanory disorders. Additional highly preferred indications include saftma and include respinster diseases (e.g., and for minder respinsters diseases (e.g., and include s and include respinsters diseases (e.g., and includers and  | myeloma, plasmacytoma, leukemia, |
|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
|                                                                 | cells and has strong effects on Blees, the PMAT. III. 24 induced by I production (Light, Pales a note in mutuced Jgf. production (Light, Pales a note in medical manufaction). The programment of leases, plasma-cytomas, mychoraes, and chronic for immunomodulatory and chronic for immunomodulatory and chronical pales and my be used or routinely modified by cytolicies, growth factors, and may be used or routinely modified to assess the manufaction (including antibodies of the invention) (including antibodies of the invention) to mediate Cell invention). Exemplary assays that test for inventions or or Teel Induction and differentiation and modulate Cell intercentiants or Teel production and transfer and the stimulation and upregulation of Teel production and transfer and the stimulation and purgulation of Teel production and the stimulation and underlying a not the stimulation and underlying so such the spreakers of the stimulation and mutucing a deligention of every the preduction of eytodries, such as an underlying a such the stimulation and mutucing a deligention and resist or manufaction of eytodries, such as such as such as an and the stimulation and mutucing and the stimulation and the stimulation and the stimulation and mutucing and the stimulation and t | and diffferentiation activity of |
|                                                                 | Production of IL-6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                  |
|                                                                 | 217                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                  |
|                                                                 | SACRAIN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                  |
|                                                                 | 108                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                  |

| described below under a described below under the pulp-pulpona, meltered biodes."). Highly preferred indications include a populsars and cause a consoliars and cause a personal and personal pe | A highly preferred indication is diabetes mellitus.  An additional highly preferred indication is a complication associated with diabetes (e.g., diabeteic retinopathy,          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (including anabodies and agoniss or anabodies and agoniss or anabodies and agoniss or anaponiss of the invention) include assays disclosed in Miraglia et al., J Bondockard Eventing 4; 193.  204(1993), Rowland et al., Tymphocytes: a practical approach?  "Lymphocytes: a practical approach" of a proper ef; 183; 160 (2000), and Verhassel et al., J Immunol of each of which are been of each of which are been only a proper ef; 182; 195; 195; 295; 195; 195; 195; 195; 195; 195; 195; 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Assays for the regulation of<br>transcription through the FAS<br>promoter element are well-known in<br>the art and may be used or routinely<br>modified to assess the ability of |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Regulation of<br>transcription through<br>the FAS promoter<br>element in hepatocytes                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 512                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HJPAD75                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 108                                                                                                                                                                              |

| motivation of the interestion                  | dishortio nombromorther bidnor disconn |
|------------------------------------------------|----------------------------------------|
| polypeptures of the myenton                    | diagenc nephilopanis, kinney disease   |
| (Including antibodies and agonists or          | (e.g., renai failure, nepnropainy      |
| antagonists of the invention) to               | and/or other diseases and disorders as |
| activate the FAS promoter element in           | described in the "Renal Disorders"     |
| a reporter construct and to regulate           | section below), diabetic neuropathy,   |
| transcription of FAS, a key enzyme             | nerve disease and nerve damage         |
| for lipogenesis. FAS promoter is               | (e.g., due to diabetic neuropathy),    |
| regulated by many transcription                | blood vessel blockage, heart disease,  |
| factors including SREBP. Insulin               | stroke, impotence (e.g., due to        |
| increases FAS gene transcription in            | diabetic neuropathy or blood vessel    |
| livers of diabetic mice. This                  | blockage), seizures, mental            |
| stimulation of transcription is also           | confusion, drowsiness, nonketotic      |
| somewhat glucose dependent.                    | hyperglycemic-hyperosmolar coma,       |
| Exemplary assays that may be used              | cardiovascular disease (e.g., heart    |
| or routinely modified to test for FAS          | disease, atherosclerosis,              |
| promoter element activity (in                  | microvascular disease, hypertension,   |
| hepatocytes) by polypeptides of the            | stroke, and other diseases and         |
| invention (including antibodies and            | disorders as described in the          |
| agonists or antagonists of the                 | "Cardiovascular Disorders" section     |
| invention) include assays disclosed in         | below), dyslipidemia, endocrine        |
| Xiong, S., et al., Proc Natl Acad Sci          | disorders (as described in the         |
| U.S.A., 97(8):3948-53 (2000);                  | "Endocrine Disorders" section          |
| Roder, K., et al., Eur J Biochem,              | below), neuropathy, vision             |
| 260(3):743-51 (1999); Oskouian B,              | impairment (e.g., diabetic retinopathy |
| et al., Biochem J, 317 (Pt 1):257-65           | and blindness), ulcers and impaired    |
| (1996); Berger, et al., Gene 66:1-10           | wound healing, and infection (e.g.,    |
| (1988); and, Cullen, B., et al.,               | infectious diseases and disorders as   |
| Methods in Enzymol. 216:362–368                | described in the "Infectious           |
| (1992), the contents of each of which          | Diseases" section below, especially    |
| is herein incorporated by reference in         | of the urinary tract and skin), carpal |
| its entirety. Hepatocytes that may be          | tunnel syndrome and Dupuytren's        |
| used according to these assays, such           | contracture). An additional            |
| as H4IIE cells, are publicly available         | highly preferred indication is obesity |
| (e.g., through the ATCC <sup>TM</sup> ) and/or | and/or complications associated with   |
| may be routinely generated.                    | obesity. Additional highly preferred   |
| Exemplary hepatocytes that may be              | indications include weight loss or     |
| used according to these assays                 | alternatively, weight gain.            |

| production. An alternative highly    | preferred embodiment of the         | invention includes a method for | inhibiting (e.g., reducing) IL-6 | production. A highly preferrred       | indication is the stimulation or   | enhancement of mucosal immunity. | Highly preferred indications include | blood disorders (e.g., as described | below under "Immune Activity",  | "Blood-Related Disorders", and/or    | "Cardiovascular Disorders"), and       | infection (e.g., as described below | under "Infectious Disease"). Highly | preferred indications include       | autoimmune diseases (e.g.,       | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis   | and/or as described below) and | immunodeficiencies (e.g., as | described below). Highly preferred | indications also include boosting a B | cell-mediated immune response and |                                | -                                  | preferred indications include        | inflammation and inflammatory | disorders. Additional highly preferred | indications include asthma and  | allergy. Highly preferred indications | include neoplastic diseases (e.g., | myeloma, plasmacytoma, leukemia, | lymphoma, melanoma, and/or as | described below under                 | "Hyperproliferative Disorders").      | Highly preferred indications include   | neoplasms and cancers, such as, |
|--------------------------------------|-------------------------------------|---------------------------------|----------------------------------|---------------------------------------|------------------------------------|----------------------------------|--------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------|------------------------------|------------------------------------|---------------------------------------|-----------------------------------|--------------------------------|------------------------------------|--------------------------------------|-------------------------------|----------------------------------------|---------------------------------|---------------------------------------|------------------------------------|----------------------------------|-------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|
| induced IgE production and increases | IgA production (IgA plays a role in | mucosal immunity). IL-6 induces | cytotoxic T cells. Deregulated   | expression of IL-6 has been linked to | autoimmune disease, plasmacytomas, | myelomas, and chronic            | hyperproliferative diseases. Assays  | for immunomodulatory and            | differentiation factor proteins | produced by a large variety of cells | where the expression level is strongly | regulated by cytokines, growth      | factors, and hormones are well      | known in the art and may be used or | routinely modified to assess the | ability of polypeptides of the       | invention (including antibodies and | agonists or antagonists of the | invention) to mediate        | immunomodulation and               | differentiation and modulate T cell   | proliferation and function.       | Exemplary assays that test for | immunomodulatory proteins evaluate | the production of cytokines, such as | IL-6, and the stimulation and | upregulation of T cell proliferation   | and functional activities. Such | assays that may be used or routinely  | modified to test immunomodulatory  | and diffferentiation activity of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Miraglia et al., J | Biomolecular Screening 4:193-   |
|                                      |                                     |                                 |                                  |                                       |                                    |                                  |                                      |                                     |                                 |                                      |                                        |                                     |                                     |                                     |                                  |                                      |                                     |                                |                              |                                    |                                       |                                   |                                |                                    |                                      |                               |                                        |                                 |                                       |                                    |                                  |                               |                                       |                                       |                                        |                                 |
|                                      |                                     |                                 |                                  |                                       |                                    |                                  |                                      |                                     |                                 |                                      |                                        |                                     |                                     |                                     |                                  |                                      |                                     |                                |                              |                                    |                                       |                                   |                                |                                    |                                      |                               |                                        |                                 |                                       |                                    |                                  |                               |                                       |                                       |                                        |                                 |

|     |         |     |                         | 204(1999); Rowland et al.,<br>"Lymphocytes: a practical approach" | myeloma, plasmacytoma, leukemia,<br>lymphoma, melanoma, and prostate, |
|-----|---------|-----|-------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------|
|     |         |     |                         | Chapter 6:138-160 (2000); and<br>Verhasselt et al. I Imminol      | breast, lung, colon, pancreatic,                                      |
|     |         |     |                         | 158:2919-2925 (1997), the contents                                | urinary cancer. Other preferred                                       |
|     |         |     |                         | of each of which are herein                                       | indications include benign                                            |
|     |         |     |                         | incorporated by reference in its                                  | dysproliferative disorders and pre-                                   |
|     |         |     |                         | entirety. Human dendritic cells that                              | neoplastic conditions, such as, for                                   |
|     |         |     |                         | may be used according to these                                    | example, hyperplasia, metaplasia,                                     |
|     |         |     |                         | assays may be isolated using                                      | and/or dysplasia. Freterred                                           |
|     |         |     |                         | techniques disclosed nerem or                                     | indications include anerma,                                           |
|     |         |     |                         | dondritio colle con continuo                                      | pancyopena, renkopenia,                                               |
|     |         |     |                         | celle in commercion culture which                                 | dicace conta lumphomic enamic                                         |
|     |         |     |                         | when activated by antiana and/or                                  | (ALL) multiple muclema Burkitt's                                      |
|     |         |     |                         | extokines initiate and unregulate T                               | lymphoma arthritis AIDS                                               |
|     |         |     |                         | cell proliferation and functional                                 | granulomatous disease inflammatory                                    |
|     |         |     |                         | activities.                                                       | bowel disease, sepsis, neutropenia,                                   |
|     |         |     |                         |                                                                   | neutrophilia, psoriasis, suppression                                  |
|     |         |     |                         |                                                                   | of immune reactions to transplanted                                   |
|     |         |     |                         |                                                                   | organs and tissues, hemophilia,                                       |
|     |         |     |                         |                                                                   | hypercoagulation, diabetes mellitus,                                  |
|     |         |     |                         |                                                                   | endocarditis, meningitis, and Lyme                                    |
|     |         |     |                         |                                                                   | Disease. An additional preferred                                      |
|     |         |     |                         |                                                                   | indication is infection (e.g., an                                     |
|     |         |     |                         |                                                                   | infectious disease as described below                                 |
|     |         |     |                         |                                                                   | under "Infectious Disease").                                          |
|     | HKABZ65 | 513 | Activation of           | Kinasc assay. JNK and p38 kinasc                                  | A highly preferred embodiment of                                      |
| 109 |         |     | Endothelial Cell p38 or | assays for signal transduction that                               | the invention includes a method for                                   |
|     |         |     | JNK Signaling           | regulate cell proliferation, activation,                          | stimulating endothelial cell growth.                                  |
|     |         |     | Pathway.                | or apoptosis are well known in the art                            | An alternative highly preferred                                       |
|     |         |     |                         | and may be used or routinely                                      | embodiment of the invention                                           |
|     |         |     |                         | modified to assess the ability of                                 | includes a method for inhibiting                                      |
|     |         |     |                         | polypeptides of the invention                                     | endothelial cell growth. A highly                                     |
|     |         |     |                         | (including antibodies and agonists or                             | preferred embodiment of the                                           |
|     |         |     |                         | antagonists of the invention) to                                  | invention includes a method for                                       |
|     |         |     |                         | promote or inhibit cell proliferation,                            | stimulating endothelial cell                                          |

|                                                                                                                | proliferation. An alternative highly<br>preferred embodiment of the<br>invention includes a method for |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| modified to test JNK and p38 kmase— miduced activity of polypeptides of pthe invention (including antipodies p | inhibiting endothelial cell proliferation. A highly preferred embodiment of the                        |
|                                                                                                                | invention includes a method for<br>stimulating apoptosis of endothelial                                |
| disclosed in Forrer et al., Biol Chem o 379(8-9):1101-1110 (1998): Ginna et le                                 | cells. An alternative highly preferred<br>embodiment of the invention                                  |
|                                                                                                                | includes a method for inhibiting (e.g.,                                                                |
| (1999); Kyriakis JM, Biochem Soc   d                                                                           | decreasing) apoptosis of endothelial<br>cells A highly meterned                                        |
| _                                                                                                              | lime                                                                                                   |
| skı                                                                                                            | includes a method for stimulating                                                                      |
| Mol Biol 71(3-4):4/9-500 (1999); (c)                                                                           | (e.g., increasing) endothelial cell<br>activation. An alternative highly                               |
| .9                                                                                                             | preferred embodiment of the                                                                            |
| its entirety. Endothelial cells that                                                                           | invention includes a method for                                                                        |
|                                                                                                                | inhibiting (e.g., decreasing) the                                                                      |
| assays are publicly available (e.g., a                                                                         | activation of and/or inactivating                                                                      |
|                                                                                                                | endoutenar cens. A mgmy<br>preferred embodiment of the                                                 |
|                                                                                                                | invention includes a method for                                                                        |
| thelial                                                                                                        | stimulating angiogenisis. An                                                                           |
| _                                                                                                              | alternative highly preferred                                                                           |
| s                                                                                                              | embodiment of the invention                                                                            |
|                                                                                                                | 8                                                                                                      |
|                                                                                                                | angiogenesis. A highly preferred                                                                       |
| nermeability vascular for                                                                                      | embodiment of the invention<br>includes a method for reducing                                          |
|                                                                                                                | cardiac hypertrophy. An alternative                                                                    |
|                                                                                                                | highly preferred embodiment of the                                                                     |
|                                                                                                                | invention includes a method for                                                                        |
|                                                                                                                | inducing cardiac hypertrophy.                                                                          |
|                                                                                                                | Highly preferred indications include                                                                   |
| u l                                                                                                            | neoplastic diseases (e.g., as described                                                                |

|  | below under "Hyperproliferative         |
|--|-----------------------------------------|
|  | Disorders"), and disorders of the       |
|  | cardiovascular system (e.g., heart      |
|  | disease, congestive heart failure,      |
|  | hypertension, aortic stenosis,          |
|  | cardiomyopathy, valvular                |
|  | regurgitation, left ventricular         |
|  | dysfunction, atherosclerosis and        |
|  | atherosclerotic vascular disease,       |
|  | diabetic nephropathy, intracardiac      |
|  | shunt, cardiac hypertrophy,             |
|  | myocardial infarction, chronic          |
|  | hemodynamic overload, and/or as         |
|  | described below under                   |
|  | "Cardiovascular Disorders"). Highly     |
|  | preferred indications include           |
|  | cardiovascular, endothelial and/or      |
|  | angiogenic disorders (e.g., systemic    |
|  | disorders that affect vessels such as   |
|  | diabetes mellitus, as well as diseases  |
|  | of the vessels themselves, such as of   |
|  | the arteries, capillaries, veins and/or |
|  | lymphatics). Highly preferred are       |
|  | indications that stimulate              |
|  | angiogenesis and/or                     |
|  | cardiovascularization. Highly           |
|  | preferred are indications that inhibit  |
|  |                                         |
|  | cardiovascularization. Highly           |
|  | preferred indications include           |
|  | antiangiogenic activity to treat solid  |
|  | tumors, leukemias, and Kaposi"s         |
|  | sarcoma, and retinal disorders.         |
|  | Highly preferred indications include    |
|  | neoplasms and cancer, such as,          |
|  | Kaposi"s sarcoma, hemangioma            |
|  | (capillary and cavernous), glomus       |

|  |  | tumors, telangiectasia, bacillary      |
|--|--|----------------------------------------|
|  |  | angiomatosis,                          |
|  |  | hemangioendothelioma,                  |
|  |  | angiosarcoma,                          |
|  |  | haemangiopericytoma,                   |
|  |  | lymphangioma, lymphangiosarcoma.       |
|  |  | Highly preferred indications also      |
|  |  | include cancers such as, prostate,     |
|  |  | breast, lung, colon, pancreatic,       |
|  |  | esophageal, stomach, brain, liver,     |
|  |  | and urinary cancer. Preferred          |
|  |  | indications include benign             |
|  |  | dysproliferative disorders and pre-    |
|  |  | neoplastic conditions, such as, for    |
|  |  | example, hyperplasia, metaplasia,      |
|  |  | and/or dysplasia. Highly               |
|  |  | 8                                      |
|  |  | arterial disease, such as,             |
|  |  | atherosclerosis, hypertension,         |
|  |  | coronary artery disease,               |
|  |  | inflammatory vasculitides,             |
|  |  | Reynaud"s disease and Reynaud"s        |
|  |  | phenomenom, aneurysms, restenosis;     |
|  |  | venous and lymphatic disorders such    |
|  |  | as thrombophlebitis, lymphangitis,     |
|  |  | and lymphedema; and other vascular     |
|  |  | disorders such as peripheral vascular  |
|  |  | disease, and cancer. Highly            |
|  |  | preferred indications also include     |
|  |  | trauma such as wounds, burns, and      |
|  |  | injured tissue (e.g., vascular injury  |
|  |  | such as, injury resulting from balloon |
|  |  | angioplasty, and atheroschlerotic      |
|  |  | lesions), implant fixation, scarring,  |
|  |  | ischemia reperfusion injury,           |
|  |  | rheumatoid arthritis, cerebrovascular  |
|  |  | disease, renal diseases such as acute  |

|     |         |     |                           |                                      | renal failure and osteonorosis         |
|-----|---------|-----|---------------------------|--------------------------------------|----------------------------------------|
|     |         |     |                           |                                      | Additional highly preferred            |
|     |         |     |                           |                                      | indications include stroke, graft      |
|     |         |     |                           |                                      | rejection, diabetic or other           |
|     |         |     |                           |                                      | retinopathies, thrombotic and          |
|     |         |     |                           |                                      | coagulative disorders, vascularitis,   |
|     |         |     |                           |                                      | lymph angiogenesis, sexual             |
|     |         |     |                           |                                      | disorders, age-related macular         |
|     |         |     |                           |                                      | degeneration, and treatment            |
|     |         |     |                           |                                      | /prevention of endometriosis and       |
|     |         |     |                           |                                      | related conditions. Additional highly  |
|     |         |     |                           |                                      | preferred indications include          |
|     |         |     |                           |                                      | fibromas, heart disease, cardiac       |
|     |         |     |                           |                                      | arrest, heart valve disease, and       |
|     |         |     |                           |                                      | vascular disease. Preferred            |
|     |         |     |                           |                                      | indications include blood disorders    |
|     |         |     |                           |                                      | (e.g., as described below under        |
|     |         |     |                           |                                      | "Immune Activity", "Blood-Related      |
|     |         |     |                           |                                      | Disorders", and/or "Cardiovascular     |
|     |         |     |                           |                                      | Disorders"). Preferred indications     |
|     |         |     |                           |                                      | include autoimmune diseases (e.g.,     |
|     |         |     |                           |                                      | rheumatoid arthritis, systemic lupus   |
|     |         |     |                           |                                      | erythematosis, multiple sclerosis      |
|     |         |     |                           |                                      | and/or as described below) and         |
|     |         |     |                           |                                      | immunodeficiencies (e.g., as           |
|     |         |     |                           |                                      | described below). Additional           |
|     |         |     |                           |                                      | preferred indications include          |
|     |         |     |                           |                                      | inflammation and inflammatory          |
|     |         |     |                           |                                      | disorders (such as acute and chronic   |
|     |         |     |                           |                                      | inflammatory diseases, e.g.,           |
|     |         |     |                           |                                      | inflammatory bowel disease and         |
|     |         |     |                           |                                      | Crohn's disease), and pain             |
|     |         |     |                           |                                      | management.                            |
|     | HKABZ65 | 513 | Regulation of apoptosis   | Caspase Apoptosis. Assays for        | A highly preferred indication is       |
| 109 |         |     | in pancreatic beta cells. | caspase apoptosis are well known in  | diabetes mellitus. An                  |
|     |         |     |                           | the art and may be used or routinely | additional highly preferred indication |
|     |         |     |                           | modified to assess the ability of    | is a complication associated with      |

|                                       | disease                               | ýć                                | orders as                              | ders"                              | pathy,                                | age                                | hy),                                  | lisease,                              | 0                               | vessel                              |                                       | totic                                 | coma,                                | eart                                |                                    | ension,                              |                                        |                                     | ection                             | ine                               |                                    | c                             |                                       | nopathy                               | paired                              | (e.g.,                                | ers as                              |                                | cially                                | carpal                                 | s,ua,                                  | nal                            | obesity                                | ed with                              | ејетер                               | ss or                              |
|---------------------------------------|---------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|------------------------------------|-----------------------------------|------------------------------------|-------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|--------------------------------|---------------------------------------|----------------------------------------|----------------------------------------|--------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|
| diabetic retino                       | diabetic nephropathy, kidney disease  | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy,  | nerve disease and nerve damage     | (e.g., due to diabetic neuropathy),   | clood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | ures, mental                          | confusion, drowsiness, nonketotic     | nyperglycemic-hyperosmolar coma,     | cardiovascular disease (e.g., heart | sclerosis,                         | nicrovascular disease, hypertension, | stroke, and other diseases and         | lisorders as described in the       | 'Cardiovascular Disorders" section | selow), dyslipidemia, endocrine   | disorders (as described in the     | Endocrine Disorders" section  | pathy, vision                         | mpairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g.,   | nfectious diseases and disorders as | e "Infectious                  | Diseases" section below, especially   | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's        | An additional                  | nighly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or |
| diabetes (e.g., diabetic retinopathy, | diabetic nephr                        | (e.g., renal fail                 | and/or other di                        | described in th                    | section below)                        | nerve disease                      | (e.g., due to di                      | blood vessel b                        | stroke, impote                  | diabetic neuro                      | blockage), seizures, mental           | confusion, dro                        | hyperglycemic                        | cardiovascular                      | disease, atherosclerosis,          | microvascular                        | stroke, and oth                        | disorders as de                     | "Cardiovascul                      | below), dyslip                    | disorders (as d                    | "Endocrine Di                 | below), neuropathy, vision            | impairment (e.                        | and blindness)                      | wound healing                         | infectious dise                     | described in the "Infectious   | Diseases" sect                        | of the urinary                         | tunnel syndror                         | contracture).                  | highly preferre                        | and/or complic                       | obesity. Addit                       | indications inc                    |
| polypeptides of the invention         | (including antibodies and agonists or | antagonists of the invention) to  | promote caspase protease-mediated      | apoptosis. Apoptosis in pancreatic | beta is associated with induction and | progression of diabetes. Exemplary | assays for caspase apoptosis that may | be used or routinely modified to test | capase apoptosis activity of    | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in: Loweth, AC, | et al., FEBS Lett, 400(3):285-8     | (1997); Saini, KS, et al., Biochem | Mol Biol Int, 39(6):1229-36 (1996);  | Krautheim, A., et al., Br J Pharmacol, | 129(4):687-94 (2000); Chandra J, et | al., Diabetes, 50 Suppl 1:S44-7    | (2001); Suk K, et al., J Immunol, | 166(7):4481-9 (2001); Tejedo J, et | al., FEBS Lett, 459(2):238-43 | (1999); Zhang, S., et al., FEBS Lett, | 455(3):315-20 (1999); Lee et al.,     | FEBS Lett 485(2-3): 122-126 (2000); | Nor et al., J Vasc Res 37(3): 209-218 | (2000); and Karsan and Harlan, J    | Atheroscler Thromb 3(2): 75-80 | (1996); the contents of each of which | are herein incorporated by reference   | in its entirety. Pancreatic cells that | may be used according to these | assays are publicly available (e.g.,   | through the ATCCTM) and/or may be    | routinely generated. Exemplary       | pancreatic cells that may be used  |
| polypeptid                            | (including                            | antagonist                        | promote c                              | apoptosis.                         | beta is ass                           | progressio                         | assays for                            | be used or                            | capase abo                      | polypeptid                          | (including                            | antagonist                            | the assays                           | et al., FBB                         | (1997); Sa                         | Mol Biol I                           | Krautheim                              | 129(4):68                           | al., Diabet                        | (2001); Su                        | 166(7):44                          | al., FEBS                     | (1999); Zi                            | 455(3):31:                            | FEBS Lett                           | Nor et al.,                           | (2000); an                          | Atheroscle                     | (1996); the                           | are herein                             | in its entir                           | may be us                      | assays are                             | through th                           | routinely g                          | pancreatic                         |
|                                       |                                       |                                   |                                        |                                    |                                       |                                    |                                       |                                       |                                 |                                     |                                       |                                       |                                      |                                     |                                    |                                      |                                        |                                     |                                    |                                   |                                    |                               |                                       |                                       |                                     |                                       |                                     |                                |                                       |                                        |                                        |                                |                                        |                                      |                                      |                                    |
|                                       |                                       |                                   |                                        |                                    |                                       |                                    |                                       |                                       |                                 |                                     |                                       |                                       |                                      |                                     |                                    |                                      |                                        |                                     |                                    |                                   |                                    |                               |                                       |                                       |                                     |                                       |                                     |                                |                                       |                                        |                                        |                                |                                        |                                      |                                      |                                    |
|                                       |                                       |                                   |                                        |                                    |                                       |                                    |                                       |                                       |                                 |                                     |                                       |                                       |                                      |                                     |                                    |                                      |                                        |                                     |                                    |                                   |                                    |                               |                                       |                                       |                                     |                                       |                                     |                                |                                       |                                        |                                        |                                |                                        |                                      |                                      |                                    |
|                                       |                                       |                                   |                                        |                                    |                                       |                                    |                                       |                                       |                                 |                                     |                                       |                                       |                                      |                                     |                                    |                                      |                                        |                                     |                                    |                                   |                                    |                               |                                       |                                       |                                     |                                       |                                     |                                |                                       |                                        |                                        |                                |                                        |                                      |                                      |                                    |

| alternatively, weight gain. Adminant highly preferred indications are complications associated with instilin resistance.                                                                                                                                                                                                                                                                                                                                                           | disheuses mellims. Additional highly preferred indications in purpose of mellings. Additional highly perferred indications include complications associated with disheuses (e.g. disheuses regularly disheuses (e.g. disheuse regularly disheuse and there dismange described in the "Reand Disorders" accurate helyon, disheute memogality are vet diseases and there dismange companies, important diseases, memal confusion, drowsitness, drows dred disserters as described in the dissorders as described in the deliventer are describ |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| according to these seasys include<br>RRAm. RNAm is not authorized<br>pancreatic beta cell insulinoma cell<br>include to beta cell insulinoma cell<br>include discontinuation in the<br>transplantable rat islet cell tumor.<br>The cells protube and secrete islet<br>polypeptide bormones, and produce<br>insulin, somatostatin, and possibly<br>gategon. ATT: CERL-2097<br>Chick et al. Proc. Natl. Acad. Sci.<br>7177 44658, Act et al. Proc. Natl.<br>Acad. Sci. 1980 77:3519. | transacription through the DMEFI transacription through the DMEFI transacription through the DMEFI the start and may be used or routinely the art and may be used or routinely the art and may be used or routinely polypeptides of the invention lo polypeptides of the invention lo extra the DMEFI response antagonists of the invention lo extra the DMEFI response that containing the GLU44 promoters and organize in the GLU74 promoters and organize in the GLU74 promoters and organize in the GLU74 promoter and bride to WHEP promoter and bride to will be used or man and the expression in skeledal mussel. CLUT is the primary mainline responsive glucose transporter in file and muss be used or routinely element advisity for adipocycles and element advisity fin adipocycles and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Regulation of transcription via DMFI responsas debranet in adhoesyles and pre-adipocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 41.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | IIKAQDS8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| 1 011 | transcription through     | transcription through the Serum              | invention includes a method for        |
|-------|---------------------------|----------------------------------------------|----------------------------------------|
|       | serum response element    | Response Element (SRE) are well-             | inhibiting (e.g., reducing) TNF alpha  |
|       | in immune cells (such     | known in the art and may be used or          | production. An alternative highly      |
|       | as natural killer cells). | routinely modified to assess the             | preferred embodiment of the            |
|       |                           | ability of polypeptides of the               | invention includes a method for        |
|       |                           | invention (including antibodies and          | stimulating (e.g., increasing) TNF     |
|       |                           | agonists or antagonists of the               | alpha production. Preferred            |
|       |                           | invention) to regulate serum                 | indications include blood disorders    |
|       |                           | response factors and modulate the            | (e.g., as described below under        |
|       |                           | expression of genes involved in              | "Immune Activity", "Blood-Related      |
|       |                           | growth and upregulate the function           | Disorders", and/or "Cardiovascular     |
|       |                           | of growth-related genes in many cell         | Disorders"), Highly preferred          |
|       |                           | types. Exemplary assays for                  | indications include autoimmune         |
|       |                           | transcription through the SRE that           | diseases (e.g., rheumatoid arthritis,  |
|       |                           | may be used or routinely modified to         | systemic lupus erythematosis,          |
|       |                           | test SRE activity of the polypeptides        | Crohn's disease, multiple sclerosis    |
|       |                           | of the invention (including antibodies       | and/or as described below),            |
|       |                           | and agonists or antagonists of the           | immunodeficiencies (e.g., as           |
|       |                           | invention) include assays disclosed in       | described below), boosting a T cell-   |
|       |                           | Berger et al., Gene 66:1-10 (1998);          | mediated immune response, and          |
|       |                           | Cullen and Malm, Methods in                  | suppressing a T cell-mediated          |
|       |                           | Enzymol 216:362-368 (1992);                  | immune response. Additional highly     |
|       |                           | Henthorn et al., Proc Natl Acad Sci          | preferred indications include          |
|       |                           | USA 85:6342-6346 (1988); Benson              | inflammation and inflammatory          |
|       |                           | et al., J Immunol 153(9):3862-3873           | disorders, and treating joint damage   |
|       |                           | (1994); and Black et al., Virus Genes        | in patients with rheumatoid arthritis. |
|       |                           | 12(2):105-117 (1997), the content of         | An additional highly preferred         |
|       |                           | each of which are herein                     | indication is sepsis. Highly           |
|       |                           | incorporated by reference in its             | preferred indications include          |
|       |                           | entirety. T cells that may be used           | neoplastic diseases (e.g., leukemia,   |
|       |                           | according to these assays are publicly       | lymphoma, and/or as described          |
|       |                           | available (e.g., through the                 | below under "Hyperproliferative        |
|       |                           | ATCC <sup>TM</sup> ). Exemplary T cells that | Disorders"). Additionally, highly      |
|       |                           | may be used according to these               | preferred indications include          |
|       |                           | assays include the NK-YT cell line,          | neoplasms and cancers, such as, for    |
|       |                           | which is a human natural killer cell         | example, leukemia, lymphoma,           |
|       |                           | line with cytolytic and cytotoxic            | melanoma, glioma (e.g., malignant      |

|     |         |     |                         | activity                                | eliona) solid filmors and mostate      |
|-----|---------|-----|-------------------------|-----------------------------------------|----------------------------------------|
|     |         |     |                         |                                         | breast line colon nancreatic           |
|     |         |     |                         |                                         | esophageal, stomach, brain, liver and  |
|     |         |     |                         |                                         | urinary cancer. Other preferred        |
|     |         |     |                         |                                         | indications include benign             |
|     |         |     |                         |                                         | dysproliferative disorders and pre-    |
|     |         |     |                         |                                         | neoplastic conditions, such as, for    |
|     |         |     |                         |                                         | example, hyperplasia, metaplasia,      |
|     |         |     |                         |                                         | and/or dysplasia. Preferred            |
|     |         |     |                         |                                         | indications include anemia,            |
|     |         |     |                         |                                         | pancytopenia, leukopenia,              |
|     |         |     |                         |                                         | thrombocytopenia, Hodgkin's            |
|     |         |     |                         |                                         | disease, acute lymphocytic anemia      |
|     |         |     |                         |                                         | (ALL), plasmacytomas, multiple         |
|     |         |     |                         |                                         | myeloma, Burkitt's lymphoma,           |
|     |         |     |                         |                                         | arthritis, AIDS, granulomatous         |
|     |         |     |                         |                                         | disease, inflammatory bowel disease,   |
|     |         |     |                         |                                         | neutropenia, neutrophilia, psoriasis,  |
|     |         |     |                         |                                         | suppression of immune reactions to     |
|     |         |     |                         |                                         | transplanted organs and tissues,       |
|     |         |     |                         |                                         | hemophilia, hypercoagulation,          |
|     |         |     |                         |                                         | diabetes mellitus, endocarditis,       |
|     |         |     |                         |                                         | meningitis, Lyme Disease, cardiac      |
|     |         |     |                         |                                         | reperfusion injury, and asthma and     |
|     |         |     |                         |                                         | allergy. An additional preferred       |
|     |         |     |                         |                                         | indication is infection (e.g., an      |
|     |         |     |                         |                                         | infectious disease as described below  |
|     |         |     |                         |                                         | under "Infectious Disease").           |
|     | HKAEV06 | 515 | Regulation of viability | Assays for the regulation of viability  | A highly preferred indication is       |
| 111 |         |     | and proliferation of    | and proliferation of cells in vitro are | diabetes mellitus. An additional       |
|     |         |     | pancreatic beta cells.  | well-known in the art and may be        | highly preferred indication is a       |
|     |         |     |                         | used or routinely modified to assess    | complication associated with           |
|     |         |     |                         | the ability of polypeptides of the      | diabetes (e.g., diabetic retinopathy,  |
|     |         |     |                         | invention (including antibodies and     | diabetic nephropathy, kidney disease   |
|     |         |     |                         | agonists or antagonists of the          | (e.g., renal failure, nephropathy      |
|     |         |     |                         | invention) to regulate viability and    | and/or other diseases and disorders as |
|     |         |     |                         | proliferation of pancreatic beta cells. | described in the "Renal Disorders"     |

| section below). diabetic neuropathy. | nerve disease and nerve damage   | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to   | diabetic neuropathy or blood vessel | blockage), seizures, mental         | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart    | disease, atherosclerosis,        | microvascular disease, hypertension,  | stroke, and other diseases and        | disorders as described in the           | "Cardiovascular Disorders" section  | below), dyslipidemia, endocrine | disorders (as described in the     | "Endocrine Disorders" section         | below), neuropathy, vision             | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g.,  | infectious diseases and disorders as | described in the "Infectious   | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's | contracture). An additional highly | preferred indication is obesity and/or | complications associated with      | obesity. Additional highly preferred  | indications include weight loss or | alternatively, weight gain. Additional | highly preferred indications are   | complications associated with insulin | resistance.                     |                                   |
|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------------|----------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|-------------------------------------|---------------------------------|------------------------------------|---------------------------------------|----------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|----------------------------------------|---------------------------------|------------------------------------|----------------------------------------|------------------------------------|---------------------------------------|------------------------------------|----------------------------------------|------------------------------------|---------------------------------------|---------------------------------|-----------------------------------|
| For example, the Cell Titer-Glo      | luminescent cell viability assay | measures the number of viable cells | in culture based on quantitation of   | the ATP present which signals the | presence of metabolically active    | cells. Exemplary assays that may be | used or routinely modified to test | regulation of viability and      | proliferation of pancreatic beta cells | by polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ohtani KI, et al., | Endocrinology, 139(1):172-8 (1998); | Krautheim A, et al, Exp Clin    | Endocrinol Diabetes, 107 (1):29-34 | (1999), the contents of each of which | is herein incorporated by reference in | its entirety. Pancreatic cells that    | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM) and/or may be    | routinely generated. Exemplary | pancreatic cells that may be used   | according to these assays include      | HITT15 Cells. HITT15 are an     | adherent epithelial cell line      | established from Syrian hamster islet  | cells transformed with SV40. These | cells express glucagon, somatostatin, | and glucocorticoid receptors. The  | cells secrete insulin, which is        | stimulated by glucose and glucagon | and suppressed by somatostatin or     | glucocorticoids. ATTC# CRL-1777 | Refs: Lord and Ashcroft. Biochem. |
| -                                    |                                  |                                     |                                       |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                         |                                     |                                 |                                    |                                       |                                        |                                        |                                     |                                      |                                      |                                |                                     |                                        |                                 |                                    |                                        |                                    |                                       |                                    |                                        |                                    |                                       |                                 |                                   |
|                                      |                                  |                                     |                                       |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                         |                                     |                                 |                                    |                                       |                                        |                                        |                                     |                                      |                                      |                                |                                     |                                        |                                 |                                    |                                        |                                    |                                       |                                    |                                        |                                    |                                       |                                 |                                   |

|                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Preferred indicious include neprincial casacsic del casac |
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| J. 219; 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | are seed known in the art and may be used known in the art and may be used and routinely modified to assess ability of polypeptides of the invention to inhibit or activate and instanction. An example of such an assay follows: Cells were percuested with SID supermatents or controls for 15-18 hours. SIAP activity was an epithelial colon adenoscration an epithelial colon adenoscration and pithelial colon adenoscration affects on the mechanism of particular states on the mechanism of for actuics on the mechanism of some actual problems of the content of specific through markers in colon cancer. See part ent. 41. Cer. Res. 89(8):732–732. | transcription through the API response for the activation of Fasswarription through the API response element are well-known in the rand may be used or roundinely modified to assess the ability of properties of the rivention of including antibodies and agonists of modified to assess the ability of properties of the rivention) to modulate growth and other cell functions. Exemplary assays for meast-plane inhaugh the API response element that may be used or response element are always.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                        | Activation of Transcription                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | remarripion (trough activation of transcription (trough activation of transcription of tran |
|                                                                                        | 21.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 818                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                        | HKAEV06                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HKAEV06                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                        | П                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | TI .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |         |     |                                | (including authorises and agoniss or authorise authorises and agoniss or authorises and agoniss or authorises authorises and agoniss or assays disclosed in Berger et al., 66 ee 66-11-0 (1988, Cullen and Malm, Methods in Fraymol Malm, Methods in Fraymol and Malm, Methods in Fraymol Park (1985, 1985). Henthorn et al., Proc Natl Acad Sci USA, 85:6342–86 (1985), Henthorn et al., Proc Natl Acad Sci USA, 85:6342–86 (1985), 1986-303 (1987), 1986-303 (1987), 1986-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1987), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 (1988), 1988-303 ( | and or as described below) and and or as described below) and and or as described below). Additional highly perferred indications include or inflammation and inflammation or indications are included ropolysatic diseases (e.g., it determit, hyphomy, and or as described below under "Hyperprodicative Diseases" (e.g., it determit, hymphomy, rostatic between, lung, colton, paracturis, essentiale all elekernial, pulmonan, postatic between, lung, colton, paracturis, essentialed, and control and contr |
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| HKAPT66   S16   Myoblast cell   Assays for masked et ploufferation   High perileration includes in the art and may be disheres, myopathy, muscle cell are well known in the art and may be disheres, myopathy, muscle cell are well known in the art and may be disheres, myopathy, muscle cell are well known in the art and may be disheres, myopathy, muscle cell are well known in the art and may be disheren; and maked each in the art and may be disheren; and maked cash in the art and may be disherent disherent and may be disherent disherent and may be disherent dish | 112 | HKAFT66 | 516 | Myoblast cell<br>proliferation | Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polynentides of the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Highly preferred indications include diabetes, myopathy, muscle cell atrophy, cancers of muscle (such as, rhabdomyona, and rhabdosaccoma).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

|  | 4 4 4                                                              |                                                                   |
|--|--------------------------------------------------------------------|-------------------------------------------------------------------|
|  | myenuon (including andoodies and                                   | Carmovascular disorders (such as                                  |
|  | agomsts or antagomsts of the<br>invention) to stimulate or inhibit | congestive near faithre, cachexia,<br>myxomas fibromas congenital |
|  | myoblast cell proliferation.                                       | cardiovascular abnormalities, heart                               |
|  | Exemplary assays for myoblast cell                                 | disease, cardiae arrest, heart valve                              |
|  | proliferation that may be used or                                  | disease, vascular disease, and also as                            |
|  | routinely modified to test activity of                             | described below under                                             |
|  | polypeptides and antibodies of the                                 | "Cardiovascular Disorders"),                                      |
|  | invention (including agonists or                                   | stimulating myoblast proliferation,                               |
|  | antagonists of the invention) include,                             | and inhibiting myoblast proliferation.                            |
|  | for example, assays disclosed in:                                  |                                                                   |
|  | Soeta, C., et al. "Possible role for the                           |                                                                   |
|  | c-ski gene in the proliferation of                                 |                                                                   |
|  | myogenic cells in regenerating                                     |                                                                   |
|  | skeletal muscles of rats" Dev Growth                               |                                                                   |
|  | Differ Apr;43(2):155-64 (2001);                                    |                                                                   |
|  | Ewton DZ, ct al., "IGF binding                                     |                                                                   |
|  | proteins-4, -5 and -6 may play                                     |                                                                   |
|  | specialized roles during L6 myoblast                               |                                                                   |
|  | proliferation and differentiation" J                               |                                                                   |
|  | Endocrinol Mar, 144(3):539-53                                      |                                                                   |
|  | (1995); and, Pampusch MS, et                                       |                                                                   |
|  | al., "Effect of transforming growth                                |                                                                   |
|  | factor beta on proliferation of L6 and                             |                                                                   |
|  | embryonic porcine myogenic cells" J                                |                                                                   |
|  | Cell Physiol Jun;143(3):524-8                                      |                                                                   |
|  | (1990); the contents of each of which                              |                                                                   |
|  | are herein incorporated by reference                               |                                                                   |
|  | in their entirety. Exemplary                                       |                                                                   |
|  | myoblast cells that may be used                                    |                                                                   |
|  | according to these assays include the                              |                                                                   |
|  | rat myoblast L6 cell line. Rat                                     |                                                                   |
|  | myoblast L6 cells are an adherent rat                              |                                                                   |
|  | myoblast cell line, isolated from                                  |                                                                   |
|  | primary cultures of rat thigh muscle,                              |                                                                   |
|  | that fuse to form multinucleated                                   |                                                                   |
|  | myotubes and striated fibers after                                 |                                                                   |

|                                   | A highly preferred indication is  | birds meterred indication is a                                              | complication associated with          | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and       | disorders as described in the      | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the      | "Endocrine Disorders" section       | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious  | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's      |
|-----------------------------------|-----------------------------------|-----------------------------------------------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|----------------------------------------|--------------------------------------|
| culture in differentiation media. | Assays for measuring secretion of | misum are well-known in the art and<br>may be used or routinely modified to | assess the ability of polypeptides of | the invention (including antibodies   | and agonists or antagonists of the   | invention) to stimulate insulin   | secretion. For example, insulin        | secretion is measured by FMAT      | using anti-rat insulin antibodies.   | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000); | Salapatek, A.M., et al., Mol       | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S ct. al.,    | Journal of Biomolecular Screening,  | 4:193-204 (1999), the contents of   | each of which is herein incorporated | by reference in its entirety. | Pancreatic cells that may be used   | according to these assays are publicly | available (e.g., through the ATCCTM) |
|                                   | Insulin Secretion                 |                                                                             |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |
|                                   | 516                               |                                                                             |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |
|                                   | HKAFT66                           |                                                                             |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |
|                                   | 611                               | 7117                                                                        |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |

| diseases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | ÷                             | or stomach, brain, liver, and urinary | e tract cancers and/or as described   | below under "Hyperproliferative    | Disorders"). Other preferred    | indications include benign | ., dysproliferative disorders and pre- | _                               | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | nd thrombocytopenia, leukemias,    |                                     | _                                   | E                                    | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | _                                     | _                                      | Ť                            | Ť                                          | _                                   | _                                   | Disease.                         |                                     |                                    |                                  |                                  |             | Highly preferred indications include | _                                | Ė                                |                                  | d disease as described below under    |
|-------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------|----------------------------------------|---------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|------------------------------|--------------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------|-------------|--------------------------------------|----------------------------------|----------------------------------|----------------------------------|---------------------------------------|
| routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Henthorn et al.,   | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its    | entirety. Mast cells that may be used | according to these assays are publicly | available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary human mast | cells that may be used according to | these assays include the HMC-1 cell | line, which is an immature human | mast cell line established from the | peripheral blood of a patient with | mast cell leukemia, and exhibits | many characteristics of immature | mast cells. | This reporter assay measures         | activation of the NFAT signaling | pathway in HMC-1 human mast cell | line. Activation of NFAT in mast | cells has been linked to extokine and |
|                                     |                                   |                               |                                       |                                       |                                    |                                 |                            |                                        |                                 |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                              |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             | Activation of                        | transcription through            | NFAT response                    | element in immune                | colle (ench ac maet                   |
|                                     |                                   |                               |                                       |                                       |                                    |                                 |                            |                                        |                                 |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                              |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             | 919                                  |                                  |                                  |                                  |                                       |
|                                     |                                   |                               |                                       |                                       |                                    |                                 |                            |                                        |                                 |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                              |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             | HKAFT66                              |                                  |                                  |                                  |                                       |
|                                     |                                   |                               |                                       |                                       |                                    |                                 |                            |                                        |                                 |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                              |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             |                                      | 112                              |                                  |                                  |                                       |

| according to these assays are publicly of firmune reactions to transplanted variable (e.g., through the reaction of transplanted reactions) and transplanted variable (e.g., through the reaction of the react | vitroning whether prediction is included an array be plately prediction in any prediction in a mark be a plately prediction in a no nesses complication associated with of the diseased complication associated with diseased diseased diseased diseased diseased diseased diseased diseased diseased disease in disease in diseases and diseases and diseased before the certain before it in the "Ream! Disorders" colio secution beloot, plately and more diseases and tenre damage before the secution beloot, plately and more diseases and tenre damage mains the seases thought, plately and properties and the certain control and the certain |
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| according to these assays are public; available (e.g., through the area ATCCVV). Exemplery human mast cells that may be used according to these assays include the HMC. Tell thus, which is an immanure human must cell line established from the persphera blood of a painten with must cell lenkerma, and exhibits must cell lenkerma, and exhibits must cell lenkerma, and exhibits must cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Regulation of viability and poulicration of cells in vitro and poulicration of cells in vitro and pulicration of cells in vitro are red-flowny in the art and may be sued or rounishy modified to assess the shility of polypoptides of the investion of the definity of polypoptides of the investion of the definity and sponitises of the investion of patencial degrades whelling and populicration of patencials of the investions to the agust a viability and populicration of patencials beta cells, in culture based on quantitation of in culture based on quantitation of the ATP present which signals the presence of metabolically active cless controlled and the controlled to test regulation of viability active cless controlled to test regulation of viability active cless recurring a governor in clouding analysis of the invention (including analysis of the invention) include anagonists of the invention) include (including analysis of the invention) include anagonists of the invention) include (including analysis of the invention) include                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | IKBHES7 817 Repair                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 113                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| The John Chem Pattern Strategy and Chem Strategy and Decease and John Chem Strategy and Decease and Depaytors is contracturely. An additional highly preferred indications associated with Chem Strategy and Complexions associated with Chem Strategy and C | so for cleans that cleans that cleans that cleans that cleans the cleans are seen the cleans are seen the cleans are clea |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | RANTES PRATA. Assays for immunonodulatory proteins that (sout is almost elemental) induce demonstrates of T Cells, annuabiliest vein immunonodulatory end cosinopilis are vein immunonosis of T Cells. Innoneosyce, and cosinopilis are vein important in concorper, and cosinopilis are vein induceducial cells. Innoneosyce, and cosinopilis are veintied to include the contract of the protein of projectives of the immunonodulation, induce contraction of cell-mediated immunity.  Coll-mediated immunity.  Coll-mediated immunity.  Coll-mediated immunity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HKB1E57 517                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 113                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly preferred indication is diabetee mellins. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopalty, diadectic retinopalty, diadectic respinopalty, kidney disease (e.g., read failure, nephropalty)                            |
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| cells. Such asseys that may be used or routinely modified to test or polypeptides of the invention of polypeptides of the invention) mediated and all submortant acreaming 4:193—184 (1993); Routinel 6:210–210, 193 (1993); Routinel 6:210–210, 193 (1993); Routinel 6:210, 193 (1993); Man (Soutinel 6:210, 210, 210); and (Soutinel 6:210, 210); and (Soutinel 7:210); and (Soutinel 7:210) | Assays for the regulation of transcription of Malle Enzyma are well-known in the art and may be used or routinely modified to assess the ability or polypeptides of the invention (including antibodies and amention (including antibodies or antisponiss or the agonisis or antisponiss of the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Regulation of transcription of Malic Enzyme in adipocytes                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 518                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | НКFВС53                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 114                                                                                                                                                                                                                                                                                             |

|  | to notiniary and an analysis of (notinovai   | as and/w when disasses and disasses as |
|--|----------------------------------------------|----------------------------------------|
|  | Malic Enzyme, a key enzyme in                | described in the "Renal Disorders"     |
|  | lipogenesis. Malic enzyme is                 | section below), diabetic neuropathy,   |
|  | involved in lipogenesisand its               | nerve disease and nerve damage         |
|  | expression is stimulted by insulin.          | (e.g., due to diabetic neuropathy),    |
|  | ME promoter contains two direct              | blood vessel blockage, heart disease,  |
|  | repeat (DR1)- like elements MEp              | stroke, impotence (e.g., due to        |
|  | and MEd identified as putative PPAR          | diabetic neuropathy or blood vessel    |
|  | response elements. ME promoter               | blockage), seizures, mental            |
|  | may also responds to AP1 and other           | confusion, drowsiness, nonketotic      |
|  | transcription factors. Exemplary             | hyperglycemic-hyperosmolar coma,       |
|  | assays that may be used or routinely         | cardiovascular disease (e.g., heart    |
|  | modified to test for regulation of           | disease, atherosclerosis,              |
|  | transcription of Malic Enzyme (in            | microvascular disease, hypertension,   |
|  | adipoocytes) by polypeptides of the          | stroke, and other diseases and         |
|  | invention (including antibodies and          | disorders as described in the          |
|  | agonists or antagonists of the               | "Cardiovascular Disorders" section     |
|  | invention) include assays disclosed          | below), dyslipidemia, endocrine        |
|  | in: Streeper, R.S., et al., Mol              | disorders (as described in the         |
|  | Endocrinol, 12(11):1778-91 (1998);           | "Endocrine Disorders" section          |
|  | Garcia-Jimenez, C., et al., Mol              | below), neuropathy, vision             |
|  | Endocrinol, 8(10):1361-9 (1994);             | impairment (e.g., diabetic retinopathy |
|  | Barroso, I., et al., J Biol Chem,            | and blindness), ulcers and impaired    |
|  | 274(25):17997-8004 (1999);                   | wound healing, and infection (e.g.,    |
|  | Ijpenberg, A., et al., J Biol Chem,          | infectious diseases and disorders as   |
|  | 272(32):20108-20117 (1997);                  | described in the "Infectious           |
|  | Berger, et al., Gene 66:1-10 (1988);         | Diseases" section below, especially    |
|  | and, Cullen, B., et al., Methods in          | of the urinary tract and skin), carpal |
|  | Enzymol. 216:362-368 (1992), the             | me a                                   |
|  | contents of each of which is herein          | contracture). An additional            |
|  | incorporated by reference in its             | highly preferred indication is obesity |
|  | entirety. Hepatocytes that may be            | and/or complications associated with   |
|  | used according to these assays are           | obesity. Additional highly preferred   |
|  | publicly available (e.g., through the        | indications include weight loss or     |
|  | ATCC <sup>TM</sup> ) and/or may be routinely | alternatively, weight gain.            |
|  | generated. Exemplary hepatocytes             | Aditional highly preferred             |
|  | that may be used according to these          | indications are complications          |

| associated with insulin resistance.                        | A highly preferred indication is a diabetes mellinas. An additional highly preferred indication is a morphication associated with diabetes (e.g., diabetic reithonpality, deliney disease (e.g., ethelici reithonpality, leadiney disease (e.g., ethelici reithonpality, leadiney disease (e.g., ethelici reithonpality, leadiney disease (e.g., eroal failture, nephropality and control other diseases and diseated as a described in the 'Renal Disoatedra's described in the 'Renal Disoatedra's active the control of the contr |
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| assays includes the H4IIE rat liver<br>hepatoma cell line. | Assays for the regulation of viability well-known in the art and may be well-known in the art and may be well-known in the art and may be and or rountinely nodified to assess the ability of polypeptides of the remotion (including antibodies and agonisis or antagonisis of the polification of puncreatic beta cells polification of puncreatic beta cells in mensions of cell Title-cit of the foremathe, the Cell Title-cit of the miniscent cell viability used polification of puncreatic beta cells in calture based on quantitation of the ATP present which signals the the ATP present which signals the cells. Exemplary usasys that may be the ATP present of the disconting of the ATP present of medicial to test regulation of viability and cells. Exemplary usasys that may be colls. Exemplary usasys that may be regulation of viability and colls. Exemplary usasys that may be regulation of viability and the or rountinely workfeet to use regulation of viability and the collicitation of the invention include by polypeptides of the invention include (1901). Housein MA, et al. (1908), Hug SR, et al., 1800 Chem (1908), Hug SR, et al. |
|                                                            | Regulation of viability and politication of paracratic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                            | 616                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                            | HKGDL36                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| g to turned syndroms and Dappsyteen's relate contraction. An additional highly complete the source and the source and the source and complete the source and the source as miderations independing preferred as a finderation in the weight focus or all of alternatively, weight gain. Additional highly preferred indications indications in the source and the source of th | ity on are consequence of a consequence |
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| cells that may be used according to these assays include or a INS1 cells.  INS1 cells are a somi-adiacent cell line established from cells isolated from an Acry induced its resistance of the control and active the cells retain characteristics typical of the cells retain characteristics typical of the cells retain characteristics typical of all cells retain characteristics typical of all cells retain characteristics typical of all cells retain characteristics to the cells including allocose inducible insulin secretion. Excernores, Ashini et al. Endocrinology 1992 1801 65.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| 133 (1974), which is herein incorporated by reference in its entirety. | RANTES FMAT. Assays for<br>immunomodulatory proteins that<br>induce chemotaxis of T cells, | monocytes, and eosinophils are well | chown in the art and may be used or<br>outinely modified to assess the | ability of polypeptides of the | nvention (including antibodies and | nycution) to mediate | mmunomodulation, induce | chemotaxis, and/or mediate humoral | or cell-mediated immunity. | Exemplary assays that test for | immunomodulatory proteins evaluate | he production of cytokines, such as | RANTES, and the induction of | chemotactic responses in immune | cells. Such assays that may be used | or routinely modified to test | mmunomodulatory activity of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Miraglia et | al., J Biomolecular Screening 4:193- | 204 (1999); Rowland et al., | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000): Cocchi et | al., Science 270(5243):1811-1815 | 1995); and Robinson et al., Clin Exp | mmumol 101(3):398-407 (1995), the | contents of each of which are herein | incomporated by reference in its |
|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------|--------------------------------|------------------------------------|----------------------|-------------------------|------------------------------------|----------------------------|--------------------------------|------------------------------------|-------------------------------------|------------------------------|---------------------------------|-------------------------------------|-------------------------------|-----------------------------|-------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-----------------------------|-------------------------------------|-------------------------------------|----------------------------------|--------------------------------------|-----------------------------------|--------------------------------------|----------------------------------|
| ii ii                                                                  | Production of RANTES Fine endothelial cells in such as human in                            | umbilical vein                      |                                                                        | 8                              |                                    | s .m                 | -14                     |                                    | 0                          |                                |                                    | <u> </u>                            |                              | 9                               | 3                                   | 0                             | -8                          | -                             |                                       | 8                                     | <u> </u>                            | e e                                  | 2                           | -                                   |                                     | 8                                |                                      | _                                 | 3                                    | -                                |
|                                                                        | 519                                                                                        |                                     |                                                                        |                                |                                    |                      |                         |                                    |                            |                                |                                    |                                     |                              |                                 |                                     |                               |                             |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                      |                                   |                                      |                                  |
|                                                                        | HKGDL36                                                                                    |                                     |                                                                        |                                |                                    |                      |                         |                                    |                            |                                |                                    |                                     |                              |                                 |                                     |                               |                             |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                      |                                   |                                      |                                  |
|                                                                        | 11.5                                                                                       |                                     |                                                                        |                                |                                    |                      |                         |                                    |                            |                                |                                    |                                     |                              |                                 |                                     |                               |                             |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                      |                                   |                                      |                                  |

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| centrey. Endotheial cells that may be used to-confing to these assys are publicly available (e.g., frough the TAC**). Exemplary excluded had cells that may be used according to cells that may be used according to vicin endotheial cells (HUVE). Which are endotheial cells (HUVE) which are endotheial cells (HUVE), which are endotheial cells (HUVE). The worked in finencians that inchid, but are not limited to, ampagenesis, but are not limited to, ampagenesis, and are most mirror and may be used in premedially yeashful and and immitted to, ampagenesis, and are most limited to, ampagenesis, and are included that the second proposed the second proposed the second proposed that the second proposed that the second proposed the second proposed that the second proposed that the second proposed the | VCAM are well-known in the art and may be used or trainingly meditied to assess the ability of polypythdes of assess the ability of polypythdes of and agonists or amagonists of the invention (including antibodies and agonists or anaponists of the revention) to regulate VCAM repression. For example, RMAT may be used to meanire the appression for clear large VCAM expression in crotherlial cells. In the control of a stance of the may be used to meanire the appreciation of clear large VCAM may be used to meanire the appreciation of a large or work of the control of the procession in endothelial cells are cells that into blood vessels, and are involved in limited to, angiogenesis, vascular polymer of the procession of VCAM immune cell cutrevisation. Exemplay endothelial cells that may be need moortified to these session include lumma unabilities! (vir memorial are vailable from commercial are vailable from |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | botherion of VCAM in cutodyclical cells consistent cells (HUVEC))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| example, hyperplasia, metaplasia,<br>and/or dysplasia.                                                                                                                                                                                                   | asthma, alluegy, hypersensitivity asthma, alluegy, hypersensitivity asthma, alluegy, hypersensitivity inflammanoy disorders. Additional inflammanoy disorders. Additional inflammanoy disorders, Additional inflammanoy disorders, disorders inflammano and hormanopoietic disorders inflamma en disorders), autoimmune inflamma en disorders), autoimmune Reinen Disorders'), autoimmune Reinen Disorders'), autoimmune Reinen Disorders'), autoimmune Reinen Disorders'), laminen soit andor as described below, andor as described below). Il galiy preferred indications as in multipe selvinential described below). Il galiy preferred indications in multe boosing or inhibiting immune cell proliferation rooplasted diseases (e.g., lotkernit) below under 'Hyperproliferative indications include boosting an eresponse, and suppressing an eresponse, and suppressing an                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| protein, can be upregulated by<br>cyclines or other fictors, and<br>contributes to the extravasation of<br>the proposition of the contributes of the<br>immune cells from blood vessels;<br>thus VCAM expression plays a role<br>inflammatory responses. | itisma easy. Whe kineas easys for signal transduction that regulate cell following the control of the control o |
|                                                                                                                                                                                                                                                          | According of July<br>Signaling Publicy of the immune cells (asch as<br>costnophils).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|                                                                                                                                                                                                                                                          | HKISB87                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                          | 116                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| be used according to these assays | include cosmopniis. Eosmopniis are | important in the late stage of allergic | reactions; they are recruited to tissues | and mediate the inflammatory | response of late stage allergic | reaction. Moreover, exemplary | assays that may be used or routinely | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to | modulate signal transduction, cell | proliferation, activation, or apoptosis | in cosinophils include assays | disclosed and/or cited in: Zhang JP, | et al., "Role of caspases in | dexamethasone-induced apoptosis | and activation of c-Jun NH2-terminal | kinase and p38 mitogen-activated | protein kinase in human eosinophils" | Clin Exp Immunol; Oct;122(1):20-7 | (2000); Hebestreit H, et al., | "Disruption of fas receptor signaling | by nitric oxide in eosinophils" J Exp | Med; Feb 2;187(3):415-25 (1998); J | Allergy Clin Immunol 1999 | Sep;104(3 Pt 1):565-74; and, Sousa | AR, et al., "In vivo resistance to | corticosteroids in bronchial asthma is | associated with enhanced | phosyphorylation of JUN N-terminal | kinase and failure of prednisolone to | inhibit JUN N-terminal kinase | phosphorylation" J Allergy Clin | Immunol; Sep;104(3 Pt 1):565-74 | (1999); the contents of each of which |
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|                                                          | A highly preferred indication is | diabetes mellitus. An             | additional highly preferred indication | is a complication associated with    | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy |                                         | _                             | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | _                                   |                                | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart  | disease, atherosclerosis,          | microvascular disease, hypertension, | stroke, and other diseases and      | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine     | disorders (as described in the  | "Endocrine Disorders" section      | below), neuropathy, vision      | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Discases" section below, especially  | of the urinary tract and skin), carpal |
| are herein incorporated by reference<br>in its entirety. | Assays for the regulation of     | transcription of Malic Enzyme are | well-known in the art and may be       | used or routinely modified to assess | the ability of polypeptides of the    | invention (including antibodies and  | agonists or antagonists of the    | invention) to regulate transcription of | Malic Enzyme, a key enzyme in | lipogenesis. Malic enzyme is         | involved in lipogenesisand its | expression is stimulted by insulin. | ME promoter contains two direct       | repeat (DR1)- like elements MEp | and MEd identified as putative PPAR | response elements. ME promoter | may also responds to AP1 and other | transcription factors. Exemplary | assays that may be used or routinely | modified to test for regulation of | transcription of Malic Enzyme (in    | adipoocytes) by polypeptides of the | invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed | in: Streeper, R.S., et al., Mol | Endocrinol, 12(11):1778-91 (1998); | Garcia-Jimenez, C., et al., Mol | Endocrinol, 8(10):1361-9 (1994);       | Barroso, I., et al., J Biol Chem,   | 274(25):17997-8004 (1999);          | ljpenberg, A., et al., J Biol Chem,  | 272(32):20108-20117 (1997);  | Berger, et al., Gene 66:1-10 (1988); | and, Cullen, B., et al., Methods in    |
|                                                          | Regulation of                    | transcription of Malic            | Enzyme in adipocytes                   |                                      |                                       |                                      |                                   |                                         |                               |                                      |                                |                                     |                                       |                                 |                                     |                                |                                    |                                  |                                      |                                    |                                      |                                     |                                     |                                    |                                     |                                 |                                    |                                 |                                        |                                     |                                     |                                      |                              |                                      |                                        |
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|                                                          | HKISB57                          |                                   |                                        |                                      |                                       |                                      |                                   |                                         |                               |                                      |                                |                                     |                                       |                                 |                                     |                                |                                    |                                  |                                      |                                    |                                      |                                     |                                     |                                    |                                     |                                 |                                    |                                 |                                        |                                     |                                     |                                      |                              |                                      |                                        |
|                                                          |                                  | 116                               |                                        |                                      |                                       |                                      |                                   |                                         |                               |                                      |                                |                                     |                                       |                                 |                                     |                                |                                    |                                  |                                      |                                    |                                      |                                     |                                     |                                    |                                     |                                 |                                    |                                 |                                        |                                     |                                     |                                      |                              |                                      |                                        |

| Exprend 2 (1545-2686 (1992), the condens of each of which is herein incorporated by reference in its entirely. Hepatodye it that may be used according to these assays are publicly without 6 (e.g. through the ATCC**) and/or may be conductly generated. Exempliar preparocytes that may be to used according to these assays neddecks that the prepared to the set assays and the prepared to the set assays and the prepared to the set assays and the set as the prepared to the set assays included to the set as a s | Regulation of visibility and positive fraction of panceasic beta cells.  Band positive fraction of positive fraction of penceasic beta cells.  Band continued modified or assess and pencention of continuely modified to assess a med or routinely modified to assess a med or routinely modified to assess and pencention (including authorides of the pencention (including authorides of the pencention) to regulate vitability and pencention of panceasis of the pencence of metabolically active of the pencence of the pencence of metabolically active of the pencence of the pen |
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| described in the "Remal Disorders"<br>section below), dishedic neuropathy,<br>nerve disease and nerve damage<br>(e.g., due to diabetic neuropathy),<br>blood vessel bloogap, heart disease,<br>stroke, imposteroe (e.g., due to<br>stroke, imposteroe (e.g., due to | diductic neuropuly or blood vessel blockage), sezizues, mental conflision, drowsiness, morketotic lyperglycemich programment comm, endrowssellar disease (e.g., heart diseases, althousellar disease, lypertension, microwascallar disease, hypertension, strong, and other diseases and strong, and other diseases and stronder and stock and other diseases and stronder and stronger and st | "Cardiovascular Disorders" section below, Apsigheniar, endocrane disorders (es described in the Tribotoriae Disorders" section Pelovo, Insurportaly, vision informent (e.g. dishetic retinopalty and blinders), latera and infrared in the control of | Diseases' section below (particularly of the urinary unet and skin). An additional highly preferred indication is obesity and/or complications is obesity and/or complications associated with obesity. Additional highly preferred indications include year, the complications are additional highly preferred indications are complications as experiently of the properties of th |
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|     |         |     |                       |                                       | the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described the many of defended by the described the most of the many o |
|-----|---------|-----|-----------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |         |     |                       |                                       | ·= ·š                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|     |         |     |                       |                                       | discase, dyslipidemia, gallstones,<br>ostcoarthritis, degenerative arthritis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|     |         |     |                       |                                       | eating disorders, fibrosis, cachexia,<br>and kidney diseases or disorders.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|     |         |     |                       |                                       | Preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|     |         |     |                       |                                       | neopiasms and cancer, such as,<br>lymphoma, leukemia and breast,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|     |         |     |                       |                                       | colon, and kidney cancer. Additional                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |         |     |                       |                                       | melanoma, prostate, lung,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|     |         |     |                       |                                       | pancreatic, csophageal, stomach,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|     |         |     |                       |                                       | brain, liver, and urinary cancer.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|     |         |     |                       |                                       | Highly preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |         |     |                       |                                       | lipomas and liposarcomas. Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|     |         |     |                       |                                       | preferred indications include benign                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |         |     |                       |                                       | dysproliferative disorders and pre-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|     |         |     |                       |                                       | neoplastic conditions, such as, for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|     |         |     |                       |                                       | example, hyperplasia, metaplasia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|     |         |     |                       |                                       | and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|     | HLDON23 | 523 | Regulation of         | Assays for the regulation of          | A highly preferred indication is                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 611 |         |     | transcription through | transcription through the PEPCK       | diabetes mellitus. An                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|     |         |     | the PEPCK promoter in | promoter are well-known in the art    | additional highly preferred indication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|     |         |     | hepatocytes           | and may be used or routinely          | is a complication associated with                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|     |         |     |                       | modified to assess the ability of     | diabetes (e.g., diabetic retinopathy,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|     |         |     |                       | polypeptides of the invention         | diabetic nephropathy, kidney disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |         |     |                       | (including antibodies and agonists or | (e.g., renal failure, nephropathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|     |         |     |                       | antagonists of the invention) to      | and/or other diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|     |         |     |                       | activate the PEPCK promoter in a      | described in the "Renal Disorders"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|     |         |     |                       | reporter construct and regulate liver | section below), diabetic neuropathy,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |         |     |                       | gluconeogenesis. Exemplary assays     | nerve disease and nerve damage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|     |         |     |                       | for regulation of transcription       | (e.g., due to diabetic neuropathy),                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| blood vessel blockage, heart disease,<br>stroke, impotence (e.g., due to | niabetic nettropamy or blood vessei<br>blockage), seizures, mental                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,<br>microvascular disease hypertension | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | Endocrine Disorders section     | impairment (e.g., diabetic retinonathy | and blindness), ulcers and impaired | wound healing, infection (e.g., an | infectious diseases or disorders as | described in the "Infectious | Diseases" section below, especially | of the urinary tract and skin), carpal | me | contracture). An additional | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | indications are disorders of the | musculoskeletal systems including<br>myonathies muscular dystronhy |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------|-----------------------------------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|---------------------------------|----------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------|-------------------------------------|----------------------------------------|----|-----------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|--------------------------------------------------------------------|
|                                                                          | test for PEPCA promoter activity (in the parocytes) of polypeptides of the bivortion (including antibodies and continuous and |                                  | .5                                  | Serger et al., Gene 66:1-10 (1998);   c                         |                                | cad Sci                       | _                                  | _                               | _                              | the content of each of which is | .5                                     |                                     |                                    | _                                   | Ť                            | liver                               | Ť                                      | _  | 9                           | -<br>e                                 | ds, insulin, or                      | SAMP derivatives.                    | i                                  |                             | 7                           |                               |                                     | 7                           |                                  |                                                                    |
| <b>4 2</b> ·                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                  |                                     |                                                                 |                                |                               | _                                  |                                 |                                |                                 |                                        |                                     | п                                  |                                     | -                            | 1                                   | 42                                     | -  | I                           | 8                                      | 2                                    | _                                    |                                    |                             |                             |                               |                                     |                             |                                  |                                                                    |
|                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                  |                                     |                                                                 |                                |                               |                                    |                                 |                                |                                 |                                        |                                     |                                    |                                     |                              |                                     |                                        |    |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                                                    |
|                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                  |                                     |                                                                 |                                |                               |                                    |                                 |                                |                                 |                                        |                                     |                                    |                                     |                              |                                     |                                        |    |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                                                    |

|     | .63 | Decelhoration of VIC AM                    | A control for a socionarian on measuration of                                 | dysprolliferative disorders and pre-<br>neoplastic conditions, such as, for<br>example, hyperplasia, metaplasia,<br>and/or dysplasia. |
|-----|-----|--------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| 523 |     | Production of VCAM<br>in endothelial cells | Assays for measuring expression of<br>VCAM are well-known in the art and      | Highly preferred indications include inflammation (acute and chronic),                                                                |
|     |     | (such as human<br>umbilical vein           | may be used or routinely modified to<br>assess the ability of polypeptides of | restnosis, atheroscierosis, asthma and<br>allergy. Highly preferred indications                                                       |
|     |     | endothelial cells                          | the invention (including antibodies                                           | include inflammation and                                                                                                              |
|     |     | (HUVEC))                                   | and agonists or antagonists of the<br>invention) to regulate VCAM             | inflammatory disorders,<br>immunological disorders, neoplastic                                                                        |
|     |     |                                            | expression. For example, FMAT                                                 | disorders (e.g. cancer/tumorigenesis),                                                                                                |
|     |     |                                            | may be used to meaure the<br>unregulation of cell surface VCAM-1              | and cardiovascular disorders (such as<br>described below under "Immine                                                                |
|     |     |                                            | expression in endothelial cells.                                              | Activity", "Blood-Related                                                                                                             |
|     |     |                                            | Endothelial cells are cells that line                                         | Disorders", "Hyperproliferative                                                                                                       |
|     |     |                                            | blood vessels, and are involved in                                            | Disorders" and/or "Cardiovascular                                                                                                     |
|     |     |                                            | limited to, angiogenesis, vascular                                            | indications include neoplasms and                                                                                                     |
|     |     |                                            | permeability, vascular tone, and                                              | cancers such as, for example,                                                                                                         |
|     |     |                                            | immine cell extravasation.                                                    | leukemia, lymphoma, melanoma,                                                                                                         |
|     |     |                                            | be used according to these assays                                             | breast, lung, colon, pancreatic,                                                                                                      |
|     |     |                                            | include human umbilical vein                                                  | esophageal, stomach, brain, liver and                                                                                                 |
|     |     |                                            | endothelial cells (HUVEC), which                                              | urinary cancer. Other preferred                                                                                                       |
|     |     |                                            | are available from commercial                                                 | indications include benign                                                                                                            |
|     |     |                                            | Sources. The expression of VCAM                                               | dysproliterative disorders and pre-                                                                                                   |
|     |     |                                            | protein, can be upregulated by                                                | example, hyperplasia, metaplasia,                                                                                                     |
|     |     |                                            | cytokines or other factors, and                                               | and/or dysplasia.                                                                                                                     |
|     |     |                                            | contributes to the extravasation of                                           |                                                                                                                                       |
|     |     |                                            | lymphocytes, leucocytes and other                                             |                                                                                                                                       |
|     |     |                                            | thing VCAM expression place a role                                            |                                                                                                                                       |
|     |     |                                            | in promoting immune and                                                       |                                                                                                                                       |
|     |     |                                            | inflammatory responses.                                                       |                                                                                                                                       |
| 523 |     | Production of ICAM-1                       | Assays for measuring expression of                                            | Preferred embodiments of the                                                                                                          |
|     |     |                                            |                                                                               |                                                                                                                                       |

| invention include using polypoptides the invention (or antibodies, agonists, or antagonists thereof) in and or creatment of inflammation, and/or returnent of inflammation, Vascular Disease, Athercosclerosis, Reserrosis, and Stroke | lighty preferred inclusions include allegy and sathma. Additional allegy and sathma. Additional allegy and sathma. Additional include immune and bromsuporietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune Related Disorders'), autoimmune Activity, and "Blood-Related Disorders"), autoimmune Related Disorders (e.g., and "Blood-Good Selective, multiple selectoris systemic lupus crytherminosis, and "Ord" signesse, multiple selectoris and/or as described below), hosting a T cell-described below), bossing a T cell-                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                        | Assays for production of II-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the ability of polypeptides and agonists or antagonists and the production of III-10 and/or activation production of III-10 and/or activation may be used or routinely modified to may be used or routinely modified to antibudies of the invention (including antibudies of the invention (including antibudies). |
|                                                                                                                                                                                                                                        | Production of T-to and activation of T-cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                        | 523                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                        | HLDON23                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 119                                                                                                                                                                                                                                    | 611                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| mediated immune response, and immune response.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | A highly preferred indication is independent of the debeces mellins. An additional highly preferred indication is a monthly preferred indication is a display preferred indication is a display preferred indication is a display preferred indication in a display preferred indication is a display preferred in a display and display d |
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| agonists or antagonists of the production and or Teetl politication include, for example, assays such as disclosed and/or Teetl politication and disclosed and/or cited in: Robinson, and the state of t | Assays for the regulation of viability and policition of cells in vito are well-known in the art and many be used or routinely modified to assess the ability of polyperpless of the invention (including antibodies and agoniss or anagoniss or that equivals or the invention (including antibodies and invention) to regulate viability and invention) to regulate viability and invention) to regulate viability and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Regulation of viability<br>and proliferation of<br>pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 524                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | нгроре2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 120                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| described in the "Renal Disorders"      | section below), diabetic neuropathy, | (e a due to diabetic neuropathy)    | (e.g., une to maneur nemopauty),<br>blood vessel blockage, heart disease. | stroke, impotence (e.g., due to   | diabetic neuropathy or blood vessel | blockage), seizures, mental         | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart    | disease, atherosclerosis,        | microvascular disease, hypertension,  | stroke, and other diseases and        | disorders as described in the         | "Cardiovascular Disorders" section   | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section        | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g.,     | infectious diseases and disorders as  | described in the "Infectious          | Diseases" section below, especially          | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture). An additional highly    | preferred indication is obesity and/or | complications associated with        | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. Additional  | highly preferred indications are       | complications associated with insulin | resistance.               |
|-----------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------------|----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|---------------------------------|--------------------------------|--------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------------|---------------------------------------|---------------------------------------|----------------------------------------------|----------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------------------|----------------------------------------|---------------------------------------|---------------------------|
| proliferation of pancreatic beta cells. | For example, the Cell Titer-Gio      | measures the number of viable cells | in culture based on quantitation of                                       | the ATP present which signals the | presence of metabolically active    | cells. Exemplary assays that may be | used or routinely modified to test | regulation of viability and      | proliferation of pancreatic beta cells | by polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Friedrichsen BN, | et al., Mol Endocrinol, 15(1):136-48 | (2001); Huotari MA, et al.,     | Endocrinology, 139(4):1494-9   | (1998); Hugl SR, et al., J Biol Chem | 1998 Jul 10;273(28):17771-9 (1998), | the contents of each of which is       | herein incorporated by reference in | its entirety. Pancreatic cells that may | be used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ) and/or may be routinely | generated. Exemplary pancreatic        | cells that may be used according to | these assays include rat INS-1 cells. | INS-1 cells are a semi-adherent cell   | line established from cells isolated | from an X-ray induced rat            | transplantable insulinoma. These   | cells retain characteristics typical of | native pancreatic beta cells including | glucose inducible insulin secretion.  | References: Asfari et al. |
|                                         |                                      |                                     |                                                                           |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                       |                                      |                                 |                                |                                      |                                     |                                        |                                     |                                         |                                       |                                       |                                              |                                        |                                     |                                       |                                        |                                      |                                      |                                    |                                         |                                        |                                       |                           |
|                                         |                                      |                                     |                                                                           |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                       |                                      |                                 |                                |                                      |                                     |                                        |                                     |                                         |                                       |                                       |                                              |                                        |                                     |                                       |                                        |                                      |                                      |                                    |                                         |                                        |                                       |                           |

|                             | Preferred indications include blood disorders (e.g., as described below |               | ely               |                                           | intection (e.g., an intectious disease | _                                | EB                              |                                     | a erythematosis, multiple sclerosis | and/or as described below),     |                                    | ment   described below), boosting a T cell- |                               | e suppressing a T cell-mediated |                                     | lies preferred indications include  | inflammation                       | .8                                     |                                     | diseases (e.g., leukemia, lymphoma, | _                           | ÷                                   | ick et Highly preferred indications include |                                |                                 | -                                  | _                                    | lymphoma, Hodgkin"s disease),    | sed melanoma, and prostate, breast, lung, | <ul> <li>blicly   colon, pancreatic, esophageal,</li> </ul> | _                            | -                                             | hese include benign dysproliferative |
|-----------------------------|-------------------------------------------------------------------------|---------------|-------------------|-------------------------------------------|----------------------------------------|----------------------------------|---------------------------------|-------------------------------------|-------------------------------------|---------------------------------|------------------------------------|---------------------------------------------|-------------------------------|---------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|-----------------------------|-------------------------------------|---------------------------------------------|--------------------------------|---------------------------------|------------------------------------|--------------------------------------|----------------------------------|-------------------------------------------|-------------------------------------------------------------|------------------------------|-----------------------------------------------|--------------------------------------|
| Endocrinology 1992 130:167. | Assays for the activation of<br>transcription through the cAMP          | _             |                   | cells). modified to assess the ability of | findleding entilodies and agonists or  | antagonists of the invention) to | increase cAMP and regulate CREB | transcription factors, and modulate | expression of genes involved in a   | wide variety of cell functions. | Exemplary assays for transcription | through the cAMP response element           | that may be used or routinely | modified to test cAMP-response  | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in         | Enzymol 216:362-368 (1992); | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Black et           | al., Virus Genes 15(2):105-117 | (1997); and Belkowski et al., J | Immunol 161(2):659-665 (1998), the | contents of each of which are herein | incorporated by reference in its | entirety. T cells that may be used        | according to these assays are publicly                      | available (e.g., through the | ATCC <sup>PM</sup> ). Exemplary mouse T cells | that may be used according to these  |
|                             | 524 Activation of<br>transcription through                              | cAMP response | element in immune | cells (such as T-cells).                  |                                        |                                  |                                 |                                     |                                     |                                 |                                    |                                             |                               |                                 |                                     |                                     |                                    |                                        |                                     |                                     |                             |                                     |                                             |                                |                                 |                                    |                                      |                                  |                                           |                                                             |                              |                                               |                                      |
|                             | HLDQR62<br>120                                                          |               |                   |                                           |                                        |                                  |                                 |                                     |                                     |                                 |                                    |                                             |                               |                                 |                                     |                                     |                                    |                                        |                                     |                                     |                             |                                     |                                             |                                |                                 |                                    |                                      |                                  |                                           |                                                             |                              |                                               |                                      |

| conditions, such as, for example, preprints, unsupplies, and/or dysplasts. Preferred indications in the form of dysplasts. Preferred indications in the form of th | thigh preferent indication is a highly preferent indication is a diabetes mellins. An additional thing preferent indication is a complication associated with diabetes (e.g., dabetic rectinopathy, idiabetes (e.g., rotal failure, replinopathy, idiabetes (e.g., rotal failure, replinopathy addition of the properties of t |
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| which is a suspension culture of IL-2 dependent cytotoxic T cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | and poulferation of cells in vitro are<br>and poulferation of cells in vitro are<br>bell-convention and are and may be<br>used or routinely modified to assess<br>the be ability of polyperatics of the<br>invention (including authorities and<br>against or antagenties of the<br>invention) to regular vability and<br>poulferation of punctatio beat cells.<br>In culture based on quantitation of<br>huminesseen cell vubility usasy<br>measures the mutuer of vable cells<br>in culture based on quantitation of<br>pressure of metabolically active<br>pressure of purchasility and<br>polyperatics of the inventor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and ponification of parameter of parameter of parameters o |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 52.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLDQU79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 121                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| nn arthy dd                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | red red                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| struck, and outer diseases and disorders as Geschiedt in the Curdinoseular Disorders' section below), dostpidermia, erdocrine blowders, dostpidermia, erdocrine blowders, dostpidermia, erdocrine blowders, erdocrine blowders, see section helboy, neuropathy, vision impairment (e.g., dilbedic retinopathy inspirator (e.g., dilbedic retinopathy inspirator (e.g., dilbedic retinopathy inspirator (e.g., dilbedic retinopathy wand belings, and infection (e.g., dilbedic retinopathy inspirator (e.g., dilbedic retinopathy inspirator (e.g., dilbedic retinopathy inspirator) (e.g., dilbedic retinopathy inspirator) (e.g., dilbedic retinopathy inspirator) (e.g., dilbedic retinopathy inspirator) (e.g., dilbedic retinopathy expection) (e.g., dilbedic retinopathy expection) (e.g., and dilbedic retinopathy preferred indications in dilbedic retinopathy experted indications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | A preferred enthodiment of the investion includes a method for inhibiting (e.g., reducing) TNF alpha production. An attenant's preferred enthodiment of the investion includes a method for simulating (e.g., investing) TNF alpha production. Preferred indications include hood disastering the graphs are production. Producted indications include hood disasters (e.g., as described below under "immune Activity"; alboda Related.                                                |
| assays disclosed in: Prioridasen BM, anguents of the Worthon Divides BM, (2001); Hustan MA, et al., Mo Indocation, 1 (101;154-8) (2001); Hustan MA, et al., Mo Indocation, 1 (101;154-8) (1995); Hug BM, et al., J Biol Chem (1998); Hug BM, et al., J Biol Chem (1998); Hug BM, et al., J Biol Chem (1998); Hug BM, and Grede of which is into contents of each of which is interest incorporated by reference in its entirety. Penceutic cells that may be to the assay are publicly worldbe (e.g., through the contents of | transcription through the Sexum<br>Response Hament (SRE) are well-<br>Response Hament (SRE) are well-<br>recommended and may be used or<br>routinely modified to assess the ele-<br>nivoration (including antibodies of the<br>invention (including antibodies and<br>invention) to explain the sexum<br>invention) to regulate the sexum<br>response Extons and modilate the<br>response Extons and modilate the<br>response Extons and modilate the<br>growth. Exemplary assessys for |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Activation of Terrascription of serior trenscription through serior response element in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 525                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | нглүүлэ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 121                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| transcri<br>may be | ranscription through the SRE that<br>may be used or routinely modified to    | Disorders"), Highly preferred indications include autoimmune |
|--------------------|------------------------------------------------------------------------------|--------------------------------------------------------------|
| test SRI           | test SRE activity of the polypeptides                                        | discases (e.g., rheumatoid arthritis,                        |
| of the ii          | of the invention (including antibodies                                       | systemic lupus erythematosis,                                |
| and ago            | and agonists or antagonists of the                                           | Crohn"s disease, multiple sclerosis                          |
| Invento            | Invention) include assays disclosed in<br>Rerort et al. Gene 66:1-10 (1998): | and/or as described below),<br>imminodeficiencies (e.g. as   |
| Cullen             | Cullen and Malm, Methods in                                                  | described below), boosting a T cell-                         |
| Enzyme             | Enzymol 216:362-368 (1992);                                                  | mediated immune response, and                                |
| Hentho             | Henthorn et al., Proc Natl Acad Sci                                          | suppressing a T cell-mediated                                |
| USA 85             | USA 85:6342-6346 (1988); and                                                 | immune response. Additional highly                           |
| Black e            | Black et al., Virus Genes 12(2):105-                                         | preferred indications include                                |
| 61) (11)           | 117 (1997), the content of each of                                           | inflammation and inflammatory                                |
| which a            | which are herein incorporated by                                             | disorders, and treating joint damage                         |
| reference          | reference in its entirety. T cells that                                      | in patients with rheumatoid arthritis.                       |
| may be             | may be used according to these                                               | An additional highly preferred                               |
| assays             | assays are publicly available (e.g.,                                         | indication is sepsis. Highly                                 |
| through            | through the ATCCTM). Exemplary                                               | preferred indications include                                |
| эsnoш              | mouse T cells that may be used                                               | neoplastic diseases (e.g., leukemia,                         |
| accordi            | according to these assays include the                                        | lymphoma, and/or as described                                |
| CLITTO             | CTLL cell line, which is an IL-2                                             | below under "Hyperproliferative                              |
| puedep             | dependent suspension culture of T                                            | Disorders"). Additionally, highly                            |
| cells wi           | cells with cytotoxic activity.                                               | preferred indications include                                |
|                    |                                                                              | neoplasms and cancers, such as, for                          |
|                    |                                                                              | example, leukemia, lymphoma,                                 |
|                    |                                                                              | melanoma, glioma (e.g., malignant                            |
|                    |                                                                              | glioma), solid tumors, and prostate,                         |
|                    |                                                                              | breast, lung, colon, pancreatic,                             |
|                    |                                                                              | esophageal, stomach, brain, liver and                        |
|                    |                                                                              | urinary cancer. Other preferred                              |
|                    |                                                                              | indications include benign                                   |
|                    |                                                                              | dysproliferative disorders and pre-                          |
|                    |                                                                              | neoplastic conditions, such as, for                          |
|                    |                                                                              |                                                              |
|                    |                                                                              | and/or dysplasia. Preferred                                  |
|                    |                                                                              | indications include anemia,                                  |
|                    |                                                                              | pancytopenia, leukopenia,                                    |

| s nuemia tiphe ma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | n n is onnal s a h h pathy, y disease thy sorders as orders as repathy, rage athy), disease, to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| thrombocytopenia, Hodgkin's ideases, acut prophocytic anemis (ALL), pleasmocytomas, multiple myclean, Bhaktir's is lymphoma andrinis, ADS, grantlomanory towed diseases, unfarmatory towed diseases, inflarmatory towed diseases, inflarmatory towed diseases, inflarmatory towed diseases, inflarmatory towed diseases, appression of immune exections to mentiopenia, hypercoagulation, diseases and expension injury, and stalma and laftergy. An additional preferred midetain is infection (e.g., an infections desse as described below indications bease as described below under "infections desses as described below under "infections desses as described below under "infections lates"). | A highly preferred indication is a diabetes relitins. An additional inhighly preferred indication is a complication associated with diabetes (e.g., diabetic retinopality, indicates (e.g., diabetic retinopality, indicates (e.g., retal failure, replinopality, indicates (e.g., retal failure, replinopality, indicates and advantage and active diabetes and distorters as accision below), diabetic ineuropality, nerve diseases and there diamege (e.g., the of indicate) indicate ineuropality, blobod vessel blockage, heart disease, stanke impronence (e.g., due to diamege remopality) diabetic ineuropality of blood vessel blockage, heart disease, stanke impronence (e.g., due to diamege remopality) diameter ineuropality of blood vessel blockage, heart disease, stanke, impronence (e.g., due to diameter disease), sezimes, unated blockage, sezimes, unated and seziment desired d    |
| dds                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | and proliferation of cells in vitro are dial<br>therebyown in the art and may be the beautiful of the beautiful |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Regulation of vibility. Assay department of and proportion of and proportion of and proportion of a proportion of a proportion of a proportion of a property of a proportion of a property of a proper    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 526                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HLHAL68                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 122                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|         |     |                    | (including antihodies and agonists or   | microvascular disease hynertension     |
|---------|-----|--------------------|-----------------------------------------|----------------------------------------|
|         |     |                    | antagonists of the invention) include   | stroke, and other diseases and         |
|         |     |                    | assays disclosed in: Friedrichsen BN,   | disorders as described in the          |
|         |     |                    | et al., Mol Endocrinol, 15(1):136-48    | "Cardiovascular Disorders" section     |
|         |     |                    | (2001); Huotari MA, et al.,             | below), dyslipidemia, endocrine        |
|         |     |                    | Endocrinology, 139(4):1494-9            | disorders (as described in the         |
|         |     |                    | (1998); Hugl SR, et al., J Biol Chem    | "Endocrine Disorders" section          |
|         |     |                    | 1998 Jul 10;273(28):17771-9 (1998),     | below), neuropathy, vision             |
|         |     |                    | the contents of each of which is        | impairment (e.g., diabetic retinopathy |
|         |     |                    | herein incorporated by reference in     | and blindness), ulcers and impaired    |
|         |     |                    | its entirety. Pancreatic cells that may | wound healing, and infection (e.g.,    |
|         |     |                    | be used according to these assays are   | infectious diseases and disorders as   |
|         |     |                    | publicly available (e.g., through the   | described in the "Infectious           |
|         |     |                    | ATCCTM) and/or may be routinely         | Diseases" section below, especially    |
|         |     |                    | generated. Exemplary pancreatic         | of the urinary tract and skin), carpal |
|         |     |                    | cells that may be used according to     | tunnel syndrome and Dupuytren's        |
|         |     |                    | these assays include rat INS-1 cells.   | contracture). An additional highly     |
|         |     |                    | INS-1 cells are a semi-adherent cell    | preferred indication is obesity and/or |
|         |     |                    | line established from cells isolated    | complications associated with          |
|         |     |                    | from an X-ray induced rat               | obesity. Additional highly preferred   |
|         |     |                    | transplantable insulinoma. These        | indications include weight loss or     |
|         |     |                    | cells retain characteristics typical of | alternatively, weight gain. Additional |
|         |     |                    | native pancreatic beta cells including  | highly preferred indications are       |
|         |     |                    | glucose inducible insulin secretion.    | complications associated with insulin  |
|         |     |                    | References: Asfari et al.               | resistance.                            |
|         |     |                    | Endocrinology 1992 130:167.             |                                        |
| HLIBD68 | 527 | Production of IL-6 | IL-6 FMAT. IL-6 is produced by T        | A highly preferred embodiment of       |
|         |     |                    | cells and has strong effects on B       | the invention includes a method for    |
|         |     |                    | cells. IL-6 participates in IL-4        | stimulating (e.g., increasing) IL-6    |
|         |     |                    | induced IgE production and increases    | production. An alternative highly      |
|         |     |                    | IgA production (IgA plays a role in     | preferred embodiment of the            |
|         |     |                    | mucosal immunity). IL-6 induces         | invention includes a method for        |
|         |     |                    | cytotoxic T cells. Deregulated          | inhibiting (e.g., reducing) IL-6       |
|         |     |                    | expression of IL-6 has been linked to   | production. A highly preferrred        |
|         |     |                    | autoimmune disease, plasmacytomas,      | indication is the stimulation or       |
|         |     |                    | myelomas, and chronic                   | enhancement of mucosal immunity.       |
|         |     |                    | hyperproliferative diseases. Assays     | Highly preferred indications include   |

|   | for immunomodulatory and               | blood disorders (e.g., as described    |
|---|----------------------------------------|----------------------------------------|
|   | differentiation factor proteins        | below under "Immune Activity",         |
|   | produced by a large variety of cells   | "Blood-Related Disorders", and/or      |
|   | where the expression level is strongly | "Cardiovascular Disorders"), and       |
|   | regulated by cytokines, growth         | infection (e.g., as described below    |
|   | factors, and hormones are well         | under "Infectious Disease"). Highly    |
|   | known in the art and may be used or    | preferred indications include          |
|   | routinely modified to assess the       | autoimmune diseases (e.g.,             |
|   | ability of polypeptides of the         | rheumatoid arthritis, systemic lupus   |
|   | invention (including antibodies and    | erythematosis, multiple sclerosis      |
|   | agonists or antagonists of the         | and/or as described below) and         |
|   | invention) to mediate                  | inmunodeficiencies (e.g., as           |
|   | immunomodulation and                   | described below). Highly preferred     |
|   | differentiation and modulate T cell    | indications also include boosting a B  |
|   | proliferation and function.            | cell-mediated immune response and      |
|   | Exemplary assays that test for         | alternatively suppressing a B cell-    |
|   | immunomodulatory proteins evaluate     | mediated immune response. Highly       |
|   | the production of cytokines, such as   | preferred indications include          |
|   | IL-6, and the stimulation and          | inflammation and inflammatory          |
|   | upregulation of T cell proliferation   | disorders. Additional highly preferred |
|   | and functional activities. Such        | indications include asthma and         |
|   | assays that may be used or routinely   | allergy. Highly preferred indications  |
|   | modified to test immunomodulatory      | include neoplastic diseases (e.g.,     |
|   | and diffferentiation activity of       | myeloma, plasmacytoma, leukemia,       |
|   | polypeptides of the invention          | lymphoma, melanoma, and/or as          |
|   | (including antibodies and agonists or  | described below under                  |
|   | antagonists of the invention) include  | "Hyperproliferative Disorders").       |
|   | assays disclosed in Miraglia et al., J | Highly preferred indications include   |
|   | Biomolecular Screening 4:193-          | neoplasms and cancers, such as,        |
|   | 204(1999); Rowland et al.,             | myeloma, plasmacytoma, leukemia,       |
| _ | "Lymphocytes: a practical approach"    | lymphoma, melanoma, and prostate,      |
|   | Chapter 6:138-160 (2000); and          | breast, lung, colon, pancreatic,       |
|   | Verhasselt et al., J Immunol           | esophageal, stomach, brain, liver and  |
|   | 158:2919-2925 (1997), the contents     | urinary cancer. Other preferred        |
|   | of each of which are herein            | indications include benign             |
|   | incorporated by reference in its       | dysproliferative disorders and pre-    |
|   | entirety. Human dendritic cells that   | neoplastic conditions, such as, for    |

| cse coumple, hyperplasia, metuplasia, referred and or obspatia. Preferred timications include arreina, future indications include arreina, future, procytogenia, Hodglari security diversity of the company of the compa | fite cells An highly perferred enhodiment of the invention includes a method and advanted by highly perferred and advanted by the invention in the art includes a method for inhibiting (e.g., of highly perferred indication is nicked by the invention of highly perferred indication is infection (e.g., an infection discussion of searched below under "Infections on the described below under "Infection of the searched bown under "Infection on the described below under "Infection on the described bown under "Infection of the described bown under "Infection on the described bown under "Infection of searched bown under "Infection |
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| may be used according to these assys rany by tablated using techniques disclosed therein or dorwise known in the art. Human clorabite cells as supervisor others, which, when activated by amigen and/or cell to supervise they are along an activities.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Production of MIP. Lalphar MACH. Assays for immunoanchalaury process for immunoanchalaury process for the upogalaury process for activated dendrific cells and upogalaury process and may be used or routinely of monoacyclomacouplage and T cell champarists are well flanown in the art and may be used or routinely of polypophics of the invention in the art and may be used or routinely of polypophics of the invention of polypophics of the invention in mediate immunoanchilation. I cell differentiation. Exemplary I cell differentiation. Exemplary I cell differentiation. Exemplary immunoanchilation of distributions such as macrophage in infammatory routeling.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 827 ILLIBD68                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 123                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| systemic lupus erythematosis,        | numpte scierosis and/or as described<br>below) and immunodeficiencies (e.g., | as described below). Additional | highly preferred indications include | inflammation and inflammatory   | disorders. Preferred indications    | also include anemia, pancytopenia, | leukopenia, thrombocytopenia,          | Hodgkin's disease, acute        | lymphocytic anemia (ALL),  | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory  | bowel disease, sepsis, neutropenia, | neutrophilia, psoriasis, suppression | of immune reactions to transplanted     | organs and tissues, hemophilia,   | hypercoagulation, diabetes mellitus,   | endocarditis, meningitis, Lyme      | Disease, asthma, and allergy.    | Preferred indications also include | neoplastic diseases (e.g., leukemia, | lymphoma, and/or as described    | below under "Hyperproliferative     | Disorders"). Highly preferred         | indications include neoplasms and | cancers, such as, leukemia,    | lymphoma, prostate, breast, lung, | colon, pancreatic, esophageal,         | stomach, brain, liver, and urinary  | cancer. Other preferred indications | include benign dysproliferative | disorders and pre-neoplastic | conditions, such as, for example, | hyperplasia, metaplasia, and/or |
|--------------------------------------|------------------------------------------------------------------------------|---------------------------------|--------------------------------------|---------------------------------|-------------------------------------|------------------------------------|----------------------------------------|---------------------------------|----------------------------|----------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------------|-------------------------------------|----------------------------------|------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|--------------------------------|-----------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------|------------------------------|-----------------------------------|---------------------------------|
| 1 alpha (MIP-1a), and the activation | of monocytes/macrophages and 1<br>cells. Such assays that may be used        | or routinely modified to test   | immunomodulatory and chemotaxis      | activity of polypeptides of the | invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed in | Miraglia et al., J Biomolecular | Screening 4:193-204(1999); | Rowland et al., "Lymphocytes: a  | practical approach" Chapter 6:138-   | 160 (2000); Satthaporn and Eremin, J | R Coll Surg Ednb 45(1):9-19 (2001); | Drakes et al., Transp Immunol        | 8(1):17-29 (2000); Verhasselt et al., J | Immunol 158:2919-2925 (1997); and | Nardelli et al., J Leukoc Biol 65:822- | 828 (1999), the contents of each of | which are herein incorporated by | reference in its entirety. Human   | dendritic cells that may be used     | according to these assays may be | isolated using techniques disclosed | herein or otherwise known in the art. | Human dendritic cells are antigen | presenting cells in suspension | culture, which, when activated by | antigen and/or cytokines, initiate and | upregulate T cell proliferation and | functional activities.              |                                 |                              |                                   |                                 |
|                                      |                                                                              |                                 |                                      |                                 |                                     |                                    |                                        |                                 |                            |                                  |                                      |                                      |                                     |                                      |                                         |                                   |                                        |                                     |                                  |                                    |                                      |                                  |                                     |                                       |                                   |                                |                                   |                                        |                                     |                                     |                                 |                              |                                   |                                 |
|                                      |                                                                              |                                 |                                      |                                 |                                     |                                    |                                        |                                 |                            |                                  |                                      |                                      |                                     |                                      |                                         |                                   |                                        |                                     |                                  |                                    |                                      |                                  |                                     |                                       |                                   |                                |                                   |                                        |                                     |                                     |                                 |                              |                                   |                                 |

| HLIBD68 | 527 | Production of TNF<br>alpha by dendritic cells | TNFa FMAT. Assays for<br>immunomodulatory proteins | A highly preferred embodiment of<br>the invention includes a method for |
|---------|-----|-----------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------|
|         |     |                                               | produced by activated macrophages,                 | inhibiting (e.g., decreasing) TNF                                       |
|         |     |                                               | T cells, fibroblasts, smooth muscle,               | alpha production. An alternative                                        |
|         |     |                                               | and other cell types that exert a wide             | highly preferred embodiment of the                                      |
|         |     |                                               | cytotoxic effects on a variety of cells            | stimulating (e.g., increasing) TNF                                      |
|         |     |                                               | are well known in the art and may be               | alpha production. Highly preferred                                      |
|         |     |                                               | used or routinely modified to assess               | indications include blood disorders                                     |
|         |     |                                               | the ability of polypeptides of the                 | (e.g., as described below under                                         |
|         |     |                                               | invention (including antibodies and                | "Immune Activity", "Blood-Related                                       |
|         |     |                                               | agonists or antagonists of the                     | Disorders", and/or "Cardiovascular                                      |
|         |     |                                               | invention) to mediate                              | Disorders"), Highly preferred                                           |
|         |     |                                               | immunomodulation, modulate                         | indications include autoimmune                                          |
|         |     |                                               | inflammation and cytotoxicity.                     | diseases (e.g., rheumatoid arthritis,                                   |
|         |     |                                               | Exemplary assays that test for                     | systemic lupus erythematosis,                                           |
|         |     |                                               | immunomodulatory proteins evaluate                 | Crohn"s disease, multiple sclerosis                                     |
|         |     |                                               | the production of cytokines such as                | and/or as described below),                                             |
|         |     |                                               | tumor necrosis factor alpha (TNFa),                | immunodeficiencies (e.g., as                                            |
|         |     |                                               | and the induction or inhibition of an              | described below), boosting a T cell-                                    |
|         |     |                                               | inflammatory or cytotoxic response.                | mediated immune response, and                                           |
|         |     |                                               | Such assays that may be used or                    | suppressing a T cell-mediated                                           |
|         |     |                                               | routinely modified to test                         | immune response. Additional highly                                      |
|         |     |                                               | immunomodulatory activity of                       | preferred indications include                                           |
|         |     |                                               | polypeptides of the invention                      | inflammation and inflammatory                                           |
|         |     |                                               | (including antibodies and agonists or              | disorders, and treating joint damage                                    |
|         |     |                                               | antagonists of the invention) include              | in patients with rheumatoid arthritis.                                  |
|         |     |                                               | assays disclosed in Miraglia et al., J             | An additional highly preferred                                          |
|         |     |                                               | Biomolecular Screening 4:193-                      | indication is sepsis. Highly                                            |
|         |     |                                               | 204(1999); Rowland et al.,                         | preferred indications include                                           |
|         |     |                                               | "Lymphocytes: a practical approach"                | neoplastic diseases (e.g., leukemia,                                    |
|         |     |                                               | Chapter 6:138-160 (2000);                          | lymphoma, and/or as described                                           |
|         |     |                                               | Verhasselt et al., Eur J Immunol                   | below under "Hyperproliferative                                         |
|         |     |                                               | 28(11):3886-3890 (1198); Dahlen et                 | Disorders"). Additionally, highly                                       |
|         |     |                                               | al., J Immunol 160(7):3585-3593                    | preferred indications include                                           |
|         |     |                                               | (1998); Verhasselt et al., J Immunol               | neoplasms and cancers, such as,                                         |
|         |     |                                               | 158:2919-2925 (1997); and Nardelli                 | leukemia, lymphoma, melanoma,                                           |

| ted.), Lettacko Biol 63:22,288 giorna (e.g. mingrama gioma), are berein incorporated by reference in diagrama gioma, his emitted in its emitory. Human dendutic cells assays may be isablactusing to these assays may be isablactusing to these assays may be isablactusing to the assays may be isablactusing the assays may be increased the ass | Assays for measuring secretion of imain are well-known in the art and infancian continual may be twacted rountinely modified to a definitional highly preferred indication assesses the shifty of polycyptides of is a complication assessed with the invention (including authodies (e.g., city of diabetic repinopathy, and agenists or antegonists of the disperse of the city of the c |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Stimulation of insulin secretion from pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 123                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| saccretion is measured by FMAT  sulpay anti-or trainin unthockies. Insulin secretion from parcratic bese cells is ingregated by glooses and also by certain protein/spepticks, and discipation is key component in disches. Exemplay sussays that may be used or notherly modified to test for stimulation of insulin secretion for the major not of the invention of the invention for themplay sussays that may polyspeptics of the invention of the protein of the invention of the protein of the invention of the protein of th | İ |                          | itibodies.   section below), diabetic neuropathy, | _                        | glucose and (e.g., due to diabetic neuropathy), | _                         | omponent in stroke, impotence (e.g., due to | ÷                      | diffed to test   blockage), seizures, mental | Ť                         | by hyperglycemic-hyperosmolar coma, | ention cardiovascular disease (e.g., heart | nd agonists or   discase, atherosclerosis, | tion) include   microvascular disease, hypertension, | ren, B., et al., stroke, and other diseases and | 2):R959-66 disorders as described in the | ndocrinology,   "Cardiovascular Disorders" section | , Kim, K.H., below), dyslipidemia, endocrine |                          | et. al., "Endocrine Disorders" section | r Screening,   below), neuropathy, vision |                         | -                       | _                          |                          | ÷                        | _                        | Ť                       | <ul> <li>ay tunnel syndrome a</li> </ul> | Ť                        | -1 cells                 | Hine and/or complications associated with | Ť                         | indications include weight loss or | s retain alternatively, weight gain. | f native Aditional highly preferred | sluding indications are complications |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |   | secretion is measured by | using anti-rat insulin an                         | Insulin secretion from p | cells is upregulated by g                       | also by certain proteins/ | disregulation is a key co                   | diabetes. Exemplary as | be used or routinely mo                      | for stimulation of insuli | (from pancreatic cells) l           | polypeptides of the inve                   | (including antibodies ar                   | antagonists of the inven                             | assays disclosed in: Ahı                        | Am J Physiol, 277(4 Pt                   | (1999); Li, M., et al., Et                         | 138(9):3735-40 (1997);                       | et al., FEBS Lett, 377(2 | (1995); and, Miraglia S                | Journal of Biomolecula                    | 4:193-204 (1999), the c | each of which is herein | by reference in its entire | Pancreatic cells that ma | according to these assay | available (e.g., through | and/or may be routinely | Exemplary pancreatic o                   | be used according to the | include rat INS-1 cells. | are a semi-adherent cell                  | established from cells is | an X-ray induced rat tra           | insulinoma. These cells              | characteristics typical o           | pancreatic beta cells inc             |

|                                                          |                               |                                 | æ                                     |                                      |                                  |                                   |                                     |                                   |                                   |                                   |                                 |                                    |                                    |                                      |                                       |                                        |                                     |                                        |                                     |                                      |                               |                                     | >                                  |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |
|----------------------------------------------------------|-------------------------------|---------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-----------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|---------------------------------|------------------------------------|------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|------------------------------------|--------------------------------------|------------------------------------|--------------------------------------|-----------------------------------------|--------------------------------|--------------------------------------|--------------------------------|--------------------------------------|---------------------------------------|----------------------------------|-----------------------------------|
|                                                          | A preferred embodiment of the | invention includes a method for | inhibiting (e.g., reducing) TNF alpha | production. An alternative preferred | embodiment of the invention      | includes a method for stimulating | (e.g., increasing) TNF alpha        | production. Preferred indications | include blood disorders (e.g., as | described below under "Immune     | Activity", "Blood-Related       | Disorders", and/or "Cardiovascular | Disorders"), Highly preferred      | indications include autoimmune       | diseases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,          | Crohn"s disease, multiple sclerosis | and/or as described below),            | immunodeficiencies (e.g., as        | described below), boosting a T cell- | mediated immune response, and | suppressing a T cell-mediated       | immune response. Additional highly | preferred indications include        | inflammation and inflammatory      | disorders, and treating joint damage | in patients with rheumatoid arthritis.  | An additional highly preferred | indication is sepsis. Highly         | preferred indications include  | neoplastic diseases (e.g., leukemia, | lymphoma, and/or as described         | below under "Hyperproliferative  | Disorders"). Additionally, highly |
| References: Astari et al.<br>Endocrinology 1992 130:167. | Assays for the activation of  | transcription through the Serum | Response Element (SRE) are well-      | known in the art and may be used or  | routinely modified to assess the | ability of polypeptides of the    | invention (including antibodies and | agonists or antagonists of the    | invention) to regulate the serum  | response factors and modulate the | expression of genes involved in | growth. Exemplary assays for       | transcription through the SRE that | may be used or routinely modified to | test SRE activity of the polypeptides | of the invention (including antibodies | and agonists or antagonists of the  | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in          | Enzymol 216:362-368 (1992);   | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); and       | Black et al., Virus Genes 12(2):105- | 117 (1997), the content of each of | which are herein incorporated by     | reference in its entirety. T cells that | may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary | mouse T cells that may be used       | according to these assays include the | CTLL cell line, which is an IL-2 | dependent suspension culture of T |
|                                                          | Activation of                 | transcription through           | serum response element                | in immune cells (such                | as T-cells).                     |                                   |                                     |                                   |                                   |                                   |                                 |                                    |                                    |                                      |                                       |                                        |                                     |                                        |                                     |                                      |                               |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |
|                                                          | 528                           |                                 |                                       |                                      |                                  |                                   |                                     |                                   |                                   |                                   |                                 |                                    |                                    |                                      |                                       |                                        |                                     |                                        |                                     |                                      |                               |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |
|                                                          | HLICQ90                       |                                 |                                       |                                      |                                  |                                   |                                     |                                   |                                   |                                   |                                 |                                    |                                    |                                      |                                       |                                        |                                     |                                        |                                     |                                      |                               |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |
|                                                          |                               | 124                             |                                       |                                      |                                  |                                   |                                     |                                   |                                   |                                   |                                 |                                    |                                    |                                      |                                       |                                        |                                     |                                        |                                     |                                      |                               |                                     |                                    |                                      |                                    |                                      |                                         |                                |                                      |                                |                                      |                                       |                                  |                                   |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | TNFa FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth masele, and other cell types that exert a wide variety of inflammatory and                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Production of TNF<br>alpha by dendritic cells                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 528                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLICQ90                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 124                                                                                                                                                                                                                                   |

| _ | extotoxic effects on a variety of cells | stimulating (e g increasing) TNF       |
|---|-----------------------------------------|----------------------------------------|
|   | are well known in the art and may be    | alpha production Highly preferred      |
|   | used or routinely modified to assess    | indications include blood disorders    |
|   | the ability of polypeptides of the      | (e.g., as described below under        |
|   | invention (including antibodies and     | "Immune Activity", "Blood-Related      |
|   | agonists or antagonists of the          | Disorders", and/or "Cardiovascular     |
|   | invention) to mediate                   | Disorders"), Highly preferred          |
|   | immunomodulation, modulate              | indications include autoimmune         |
|   | inflammation and cytotoxicity.          | diseases (e.g., rheumatoid arthritis,  |
|   | Exemplary assays that test for          | systemic lupus erythematosis,          |
|   | immunomodulatory proteins evaluate      | Crohn"s disease, multiple sclerosis    |
|   | the production of cytokines such as     | and/or as described below),            |
|   | tumor necrosis factor alpha (TNFa),     | immunodeficiencies (e.g., as           |
|   | and the induction or inhibition of an   | described below), boosting a T cell-   |
|   | inflammatory or cytotoxic response.     | mediated immune response, and          |
|   | Such assays that may be used or         | suppressing a T cell-mediated          |
|   | routinely modified to test              | immune response. Additional highly     |
|   | immunomodulatory activity of            | preferred indications include          |
|   | polypeptides of the invention           | inflammation and inflammatory          |
|   | (including antibodies and agonists or   | disorders, and treating joint damage   |
|   | antagonists of the invention) include   | in patients with rheumatoid arthritis. |
|   | assays disclosed in Miraglia et al., J  | An additional highly preferred         |
|   | Biomolecular Screening 4:193-           | indication is sepsis. Highly           |
|   | 204(1999); Rowland et al.,              | preferred indications include          |
|   | "Lymphocytes: a practical approach"     | neoplastic diseases (e.g., leukemia,   |
|   | Chapter 6:138-160 (2000);               | lymphoma, and/or as described          |
|   | Verhasselt et al., Eur J Immunol        | below under "Hyperproliferative        |
|   | 28(11):3886-3890 (1198); Dahlen et      | Disorders"). Additionally, highly      |
|   | al., J Immunol 160(7):3585-3593         | preferred indications include          |
|   | (1998); Verhasselt et al., J Immunol    | neoplasms and cancers, such as,        |
|   | 158:2919-2925 (1997); and Nardelli      | leukemia, lymphoma, melanoma,          |
|   | et al., J Leukoc Biol 65:822-828        | glioma (e.g., malignant glioma),       |
|   | (1999), the contents of each of which   | solid tumors, and prostate, breast,    |
|   | are herein incorporated by reference    | lung, colon, pancreatic, esophageal,   |
|   | in its entirety. Human dendritic cells  | stomach, brain, liver and urinary      |
|   | that may be used according to these     | cancer. Other preferred indications    |
|   | assays may be isolated using            | include benign dysproliferative        |

| ,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| disorders and pre-acoplastic conditions, such as for example, hyperplasti, metaplasti, and or depopulation, and or depopulation, and or depopulation and or depopulation and or depopulation and or depopulation and or depopulation and depopulation and depopulation and depopulation and depopulation, and depopulation and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, and depopulation, depopulation, depopulation, depopulation, depopulation, disches and depopulation, disches and depopulation, disches and depopulation, disches and depopulation and altergi. | A highly preferred indication is disheres realitims a additional highly preferred indication a additional highly preferred indication is a complication associated with diabetes (e.g., diabettic rephropathy, kidney diseases defeative methoropathy and control addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and addition and additio |
| techniques disclosed herein or develorise known in the art. Human dendritic cells are antigen presenting for in supersoin culture, which, when activated by antigen and or cold proliferation and intestinal activities.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | sasses for measuring eaching that are well-known in the art and may be used or routinely modified to assess the ability of polyperides of the invention (including antibodies and groups of a properiors or the invention (including antibodies and groups its or all the invention) to mobilize calcium. For used to measure influx of ediction. Cetample, the FLPR assay may be used to measure influx of ediction. Cells normally have very low concernations of cytosolic calcium compared to much ingher concuprated to much higher concuprated to much higher concuprated to much higher concernations of cytosolic calcium. Extracellular effective concerns as influx of edictions are with the concuprated to much higher.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| diabetic neuropathy or blood vessel<br>blockage), seizures, mental<br>confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma,<br>cardiovascular disease (e.g., heart<br>disease, atherosclerosis, | microvascular disease, hypertension,<br>stroke, and other diseases and | disorders as described in the<br>"Cardiovascular Disorders" section             | below), dyshipidemia, endocrine<br>disorders (as described in the | "Endocrine Disorders" section<br>below), neuropathy, vision    | impairment (e.g., diabetic retinopathy | and bundness), utcers and impaired<br>wound healing, and infection (e.g., | infectious diseases and disorders as  | described in the "Infectious           | Diseases" section below, especially     | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's<br>contracture) An additional | red ir                          | and/or complications associated with | obesity. Additional highly preferred | alternatively, weight gain.       | Aditional highly preferred           | indications are complications       | associated with insulin resistance. |                                       |                                    |                            |                                  |                               |                                     |
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| calcium, leading to activation of<br>calcium responsive signaling<br>pathways and alterations in cell   | functions. Exemplary assays that<br>may be used or routinely modified to<br>measure calcium flux by  | polypeptides of the invention<br>(including antibodies and agonists or | antagonists of the invention) include<br>assays disclosed in: Satin LS, et al., | Endocrinology, 136(10):4589-601<br>(1995);Mogami H, et al.,       | Endocrinology, 136(7):2960-6<br>(1995); Richardson SB, et al., | Biochem J, 288 ( Pt 3):847-51          | (1992); and, Meals, JE, et al., Cell<br>Calcium 1989 Nov-Dec:10(8):535-41 | (1989), the contents of each of which | is herein incorporated by reference in | its entirety. Pancreatic cells that may | be used according to these assays are  | ATCCTM and/or may be routinely                                | generated. Exemplary pancreatic | cells that may be used according to  | these assays include HTTT15 Cells.   | cell line established from Svrian | hamster islet cells transformed with | SV40. These cells express glucagon, | somatostatin, and glucocorticoid    | receptors. The cells secrete insulin, | which is stimulated by glucose and | glucagon and suppressed by | somatostatin or glucocorticoids. | ATTC# CRL-1777 Refs: Lord and | Ashcroft. Biochem. J. 219: 547-551; |
|                                                                                                         |                                                                                                      |                                                                        |                                                                                 |                                                                   |                                                                |                                        |                                                                           |                                       |                                        |                                         |                                        |                                                               |                                 |                                      |                                      |                                   |                                      |                                     |                                     |                                       |                                    |                            |                                  |                               |                                     |
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|                                                                    | A highly preferred indication is  | diabetes mellitus. An                 | additional highly preferred indication | is a complication associated with     | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious           | Diseases" section below, especially  | of the urinary tract and skin), carpal |
|--------------------------------------------------------------------|-----------------------------------|---------------------------------------|----------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|
| Santerre et al. Proc. Natl. Acad. Sci.<br>USA 78: 4339-4343, 1981. | Assays for measuring secretion of | insulin are well-known in the art and | may be used or routinely modified to   | assess the ability of polypeptides of | the invention (including antibodies   | and agonists or antagonists of the   | invention) to stimulate insulin   | secretion. For example, insulin        | secretion is measured by FMAT      | using anti-rat insulin antibodies.   | Insulin secretion from panercatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S et. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     |
|                                                                    | Stimulation of insulin            | secretion from                        | pancreatic beta cells.                 |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |
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|                                                                    | HLICQ90                           |                                       |                                        |                                       |                                       |                                      |                                   |                                        |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |
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| con high high high high and ope ope indi indi alte ass | sawy, for A highly perferred embodiment assawy, for of the invention includes a method man draw by the configuration. An alternative highly soft on season and may be predrated embodiment of the profits of the season includes a method for mibit cell highly preferred embodiment of the season includes a method for mibit cell with the season for the invention includes a method for mibiting adhocyte differentiation. An alternative highly preferred embodiment of the standard preferred embodiment of the standard preferred embodiment of the standard preferred embodiment of the standard for minding (e.g., increasing) on simulating (e.g., increasing) on simulating the activation of (e.g., standard for minding the activation of (e.g., presents) on bindulee and profit of the standard for minding the activation of (e.g., precision of minding the activation of (e.g., precision of minding preferred embodiment of the season of the standard for minding the activation of (e.g., precision of minding preferred embodiment of the precision of minding the activation of (e.g., precision of minding preferred embodiment of the minding season of minding the activation of (e.g., precision of minding preferred embodiment of the minding preferred embodiment of the dispospers. Highly preferred embodiment of the minding of the activation of (e.g., precision of minding preferred embodiment of the dispospers. Highly preferred embodiment of the dispospers. Highly preferred embodiment of the dispospers. Highly preferred embodiment of the dispospers. Highly preferred embodiment of the dispospers. Highly preferred embodiment of the dispospers. Highly preferred embodiment of the dispospers.                                                                                                                                                                                                                                                                                                                                                                               |
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|                                                                                                                                                                        | to these clels hard "Hyperpondicatives").  Preferred indications include blood liable (e.g., hypertaleration, congestive heard failing; blood vessel har may be bloodege, heart disease, stroke, proportee and proportee and or may be indicated as a series of the proportee and or may be indicated as a series of the proportee and or may be indicated as a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of the proportee and or a series of t |                                                                                                                                                                                                                                             | infection (e.g., sea described below under "Infections Disease").  A highly preferred indication is diabetes mellina. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic repinopathy, teach real failtier, repitropathy and/or other diseases and disorders as | described in the Verlan Disorders' section below), diabetic neuropathy, nerve disease and nerve damage to the verbase and the verbase of e.g., due to diabetic neuropathy. blood vessel blockage, heart disease, stroke, importere, cfg., due to diabetic neuropathy or blood vessel diabetic neuropathy or blood vessel diabetic neuropathy or blood vessel diabetic neuropathy or blood vessel |
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| MH, Prog Biophys Mol Biol 70(201); and Cobb MH. Prog Biophys Mol Biol 71(5)—49,479–500 (199); the contents of each of which are herein incorporated by reference in is | entiriey. Montae adjocyce elel hair<br>may be used according to these<br>assays are publicly available (e.g.,<br>through the ATTCV <sup>2</sup> ). Examplary<br>mouse adjocyce cells that may be<br>need according to these assays<br>in-shed ATTA I colle. ATTA I is soil.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | adheven mouse, preadhooyte cell line that is a continuous substrain of 373 filroblast cells erechoyed through colonia losalaoun and undergo a pre-adjuoyte to adjuose-like proversion under appropriate differentiation conditions known in | the art.                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                  |
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| confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | los | gain. Additional highly | preferred indications are | complications associated with insulin | resistance. Additional highly | preferred indications are disorders of | the musculoskeletal systems | including myopathies, muscular | dystrophy, and/or as described | herein. Additional highly | preferred indications include, | hypertension, coronary artery | disease, dyslipidemia, gallstones, |
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| eating disorders, fibrosis, cachecia, and kiney disease or disorders. Preferred indications include supplemental and organization of the propositions and complement and organization of the propositions and complemental preferred indications include preferred indications include preferred indications include particularly and proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the propositio | An highly preferred embodiment of an ether invention includes a method for production. An alternative lightly preferred embodiment of the production. An alternative lightly preferred embodiment of the revention includes a method for subtilining (e.g., reducing) MCP-1.  Sprudetion. A manufactured of the revention includes a method for an indication is infection (e.g., an include is infection (e.g., an indication is infection (e.g., an indication is infection (e.g., an indication is infection (e.g., an indication is infection (e.g., an indications include in infammation and infections lightly preferred infammation of discretes.) Preferred infammation of discretes. Preferred infammation of discretes. Preferred infammation of discretes in financiarons include biol disconters. Immune Activity. "Shood-Related Infammation discretes," and/or "Cardiovissular Infamiliarious include antoniumman. |
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| of each of which are preterior reactions to transplanted organs and incorporated by reference in its entirely. Human dendrice cells that may be to the season of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the contro | n in in its in its coels that these these in in its in its in its in its in its in its in its in its in its in its in its in in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in its in | of each of which are therein incorporated by reference in its incurrence in the remains and an enderstance of the may be used according to these assays may be isolated using techniques to reduce known in the art. Human decrative clean aemigan processing other activated by antigen and/or ophocines, infinite and upon culture, which, when cultured by antigen and/or ophocines, infinite and upon culture, which, when cultured by a major and/or ophocines, infinite and upon culture, which, when called profileration and functional activities. |
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| and difflerentiation activity of polypeptides of the invention finduling anthodies and agonisis or authorities of the invention hinded anthodies and agonisis or antendral approach of the control produced and the control produced and the control produced of the control produced of the control produced of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of t |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Production of TNF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| the invention includes a method for<br>inthiting (e.g., decreasing) TNF<br>alpha production. An alternative<br>highly preferred embodiment of the<br>invention includes a method for<br>stimulating (e.g., increasing) TNF<br>alpha production. Highly preferred | interiories include blood disorders (e.g., as described below disorders immer Activity", "Blood-Beland Disorders"). Highly preferred indications include autorimme discases (e.g., rheumatoid arthritis, choir's disease, multiple seleroris choir's disease, multiple seleroris immunodeficiencies (e.g., is immunodeficiencies (e.g., is immunodeficiencies (e.g., is                                                                                      | excitable below), bossing at cell- mediated immune response, and appressing at Cell-mediated immune response, Additional light preprint directions include inflammation and inflammatory inflammation and inflammatory inflammation and inflammatory inflammation and inflammatory inflammation and inflammatory inflammation and inflammatory inflammation and inflammatory inflammation and inflammatory inflammation and inflammation inflammation and inflammation preferred indications include proprint direction in the dis- preferred indications include Disancter's Additionally inflamy the morphora, and or as described Disancter's Additionally inflamy preferred indications include preferred indications include propriestins and cancers, such as, gliomat Ceg., multigrant glioma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| immunomodulatory proteins produced by activated macroplages, T cells, fibroblasis, smooth musele, and other cell types that exert a wide variety of inflammatory and cytoxic effects on a variety of cells are well known in the art and may be                  | the chilty of probabilities and another of usessas the chilty of probabilities of the chilty of probabilities and agonists or mangionis of the invention) to mediate, nothing mannonounditation, modulate inflammation and eyotooxicity. Templars assays that cast for immunonounditation y proteins evaluate immunounditationy proteins evaluate immunounditationy proteins evaluate the production of cyokhens such as tumor necessis factor alpha (TNFa). | inflammatory or cytowoxic response, and the induction of an inflammatory or cytowoxic response, repulse assessy that may be used or routinely modified to test mountment mediated to test invention or polypergidises of the invention polypergidises of the invention include managenists of the invention include an anagenists of the invention include Biomodecular Severaing 4:193-204(1999); Rowland et al., 204(1999); Rowland et al., Tammanol Lowrissel et al., Lan Jammanol 14, Jammanol 140(7):388-3899 (11987, Dahlene et al., Jammanol 140(7):388-3899 (1988); Verhasselt et al., Jammanol Lowrisselt et al., Jammanol 140(7):388-3899 (1988); Verhasselt et al., Jammanol Lowrisselt et al., Jammanol Lowri |
| alpha by dendritic cells                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| 125                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|     |         |     |                                                               | They), the contrasts of reach of which are berein incorporated by reference in section of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the contrast of the | lung, colon, prostate, breast, lung, colon, paracentic, esophiageal, search, brain, liver and trimage cancer. Other preferred indications include benign dosponliferative conditions, such as, for example, benign dosponliferative conditions, such as, for example, preparals amendor and or dosplasia, and or dosplasia, land or dosplasia, and control and control and an artificial monthly and an artificial monthly and an artificial monthly and artificial supportant, and trials, AIDS, bowed disease, radure presentions to tensil monthly the procubilistic, for the control of immune rections to tensil ming, endocentrilis, meninglis, Lyme of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the cont |
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| 126 | HLTHR66 | 530 | Stirmulation of insulin secretion from pancreatic beta cells. | sugasy for measuring secretion of<br>insulin are well-known in the art and<br>may be used or routinely modified to<br>may be used or routinely modified to<br>may be used or routinely modified to<br>the invention (including anthodies of<br>the invention) to simulate insulin<br>invention) to simulate insulin<br>secretion; for example, insulin<br>secretion is measured by PMAT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | A highly preferred indication is<br>diabetes mellins<br>additional highly preferred indication<br>is complication associated with<br>diabetes (e.g., diabetic retinopathy,<br>diabetes (e.g., timbetic retinopathy,<br>diese to pulpopathy, kithey disease<br>(e.g., renal inlane, nephropathy<br>is more consistent and includers as<br>described in the "Renal Disouders" as<br>described in the "Renal Disouders"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| using anti-rai insulin antibodies.  lusing anti-rai insulin antibodies.  al slab y octatin protein peptides, and also by certain potenticypelides, and disregulation is a key component in didences. Exemplary assays that may be used or routinely modified to sea!  for simulation of insulin secretion (from pancreatic cells) in the investion include assays tile-losed in. Altern. B. et al. A. and Piposa, T. App. 147 (4) 2499-46.  (1999), L. M. et al. Endocrinology.  138(9):2755-40 (1997), Knm. K. H., et al., EBBS CLEAT (2), 779, 749-74.  (1995), and Miragia Set. al., Journal of Biomotestura Secreting, Parcentice in its entirety.  Parcentice on its entirety.  Parcentice on its entirety.  Parcentice on the entirety incorporated by reference in its entirety.  Parcentic of these assays are publicly and/or may be routinely generated.  Estamplary parcentic cell inter established from cells isolated from an X-ray induced rat transplantable insulingen. These cells retainly chance in security. |
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| Hadeocuboly 1992 130-167.  Findential of the sea of the search of parameter of insulin amplied or of secretion from insulin according to which the sea of parameter of secretion from insulin according to the parameter of seasons the ability of polypeptides of the invention of the chanding analysis of the invention of the chanding analysis of the invention of the change analysis of the invention of the change analysis of the invention of the change analysis of the invention of the change analysis of the invention of the seasons the change of the change analysis of the invention of the single analysis of the invention of the invention of insulin secretion (from parameter of insulin secretion (from parameter of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insulin secretion) (from parameters of insuling secretics) (from paramet |                             | - | _ | ely modified to additional highly preferred indication | olypeptides of is a complication associated with | ng antibodies   diabetes (e.g., diabetic retinopathy, | _                                  | e insulin (e.g., renal failure, nephropathy |                       | _                     |                                    | _                                      |                                     | _                                      | _                                   | ÷                                   |                                       | Ť                                    |                            | vention cardiovascular disease (e.g., heart | -                     | _                       | hren, B., et al., stroke, and other diseases and | ÷                     | _                         | Ħ,                   | _                       | -                     |                       |                       | n incorporated and blindness), ulcers and impaired | irety. wound healing, and infection (e.g., | nay be used infectious diseases and disorders as | ays are publicly   described in the "Infectious |                                                   | ly generated of the uringry fract and ckin) compa |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Endocrinology 1992 130:167. | - |   |                                                        | assess the ability of po                         | the invention (including antibodies                   | and agonists or antagonists of the | invention) to stimulate insulin             | secretion For example | secretion is measured | using anti-rat insulin antibodies. | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by | polypeptides of the invention               | (including antibodies | antagonists of the inve | assays disclosed in: Al                          | Am J Physiol, 277(4 P | (1999); Li, M., et al., I | 138(9):3735-40 (1997 | et al., FEBS Lett, 377( | (1995); and, Miraglia | Journal of Biomolecul | 4:193-204 (1999), the | each of which is herein incorporated               | by reference in its entirety.              | Pancreatic cells that may be used                | according to these assays are publicly          | available (e.g., through the ATCC <sup>TM</sup> ) | and/or may be routinely generated.                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                             |   |   |                                                        |                                                  |                                                       |                                    |                                             |                       |                       |                                    |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                            |                                             |                       |                         |                                                  |                       |                           |                      |                         |                       |                       |                       |                                                    |                                            |                                                  |                                                 |                                                   |                                                   |

|     |         |     |                                                | the treat decording to these assays include an INS-1 cells. INS-1 cells. INS-1 cells. The same as semi-address cell include from cells isolated from an X-ray induced real transplantable and an X-ray induced real transplantable and an include from cells isolated from cells including characteristics typical of markey proceed to be a cells including places includible marilin secretion. Bridgerones, Inductive Insulin secretion. Findocrinology 1992-130-167.                                                                                                                                                                                                                                                                                                                                                                                                                                                 | contracture). An additional highly preferred indication is obesity and offer complications associated with obesity. Additional highly preferred indications include weight gain. Additional highly preferred indications are complications associated with measurements of the complications associated with insulin preferred indications are complications.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| 128 | HLWAA17 | 223 | transcription of Malie<br>Euzyme in adipocytes | transacription of Maite Enzyme are<br>well-known in the ent and may be<br>used or routinely modified to assess<br>the ability of polypspridises of the<br>merical (modified) anthodics and<br>agonists or amagonists of the<br>merical (modified) anthodics and<br>agonists or amagonists of the<br>merical (modified) anthodics and<br>agonists or amagonists of the<br>merical (modified) and the merical<br>Maite Enzyme, a key enzyme in<br>involved in lipogenesis and in<br>proposens, had merical and in-<br>merical merical and and and<br>MEI dentified as putative PPAR<br>response elements. MEI promoter<br>reasons that merical merical and other<br>may also response to be used or routinely<br>modified to est for regulation of<br>adjonestics (Mellie Enzyme (in<br>adjonestics) by polypeptides of the<br>agonists or amagonists of the<br>agonists or amagonists of a<br>agonists or amagonists of a | h highly prederect indication is diabetes mellins.  A highly predered indication and additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retimopathly discussed feels, etheric retimopathly kithey discussed (e.g., treat linitue, traphropathly and the composition of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company |

| "Indocrite Disorders" section below), neuropathy vision impainment (e.g., diabetic retinopathy and blindress), ulotes and impaired wound healing, and infection (e.g., classers) exclusion the "Infections of success and disorders as described in the "Infections to a constructure"). An additional of the uniony tract and skin), carpal countesture). An additional contracture). An additional indication is succinated with ander complications associated with indications include weight loss or alternatively, weight gain. Additional highly preferred indications include weight loss or alternatively, weight gain.                                                                                                                                                                              | referred enhodiments of the invention include using polyapsides of the invention of an anti-object and angoings, a genuis, or antagonists thereof) in decident, diagnosis, prevention and/or treatment of Inflammation, Vacular Disease, Atheroesclerosis, Resienosis, and Stroke                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Garcia-Jinnew C. et al., Mol<br>Garcia-Jinnew C. et al., Mol<br>Endocrinol. 8(10);1361-91 (1994).<br>Endocrinol. 8(10);1361-91 (1994).<br>274(23);17907-8004 (1999).<br>274(23);27004-2011 (1099).<br>Britonete, A. et al. J Biol Chem.<br>273(23);20108-2011 (1099).<br>and, Cullen. B., et al., Methods in<br>and, Cullen. B., et al., Methods in<br>and, Cullen. B., et al., Methods in<br>endocrinol. 26-26-368 (1992), the<br>contents of each of which is herein<br>and expressed et al., Methods in<br>endicity. Hepatocytes that may be<br>contents of each of which is herein<br>publicy available (e.g. through the<br>ATCCP) and the may be outnieby<br>are endered. Even may be outnieby<br>are endered. Even may be outnieby<br>are assessive includes the HHIE int inver<br>hepatoma cell line. | ICAM-1 are well-known in the art manning expression of ICAM-1 are well-known in the art modified to assess the ability of properpides of the invention of including analysis and agoniss or analysonists and agoniss or analysonists and the invention to regulate ICAM-1 copression Exemplary assays that may be used ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare ICAM-1 expression include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include usasyare and include u |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Production of ICAM-1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 532                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HLWAA17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 128                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| used the publicy to publicy ATCC", ATCC", are retreated. The treated the total collection of the public to the second to the public to the second to the public to the second to the public to the second to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the public to the pub | says, for a Neighbor preferred embodiment au regular of the invention includes a method for inhibiting adipocyte method for inhibiting adipocyte profileration. An alternative highly method for inhibiting adipocyte profileration of the inhibiting adipocyte profileration of the inhibiting adipocyte profileration inhibit cell a method for inhibiting adipocyte profileration. An alternative highly preferred mobilization of the invention includes a method for inhibiting an amount of the invention includes a method for inhibiting as it FRK highly preferred embodiment of the informative method for inhibiting and procyte differentiation. A highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred embodiment of the highly preferred for innervating discusses (e.g., as described below of 2016. Highly preferred indicate responsible size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited size-easing and cook meta-visited and cook meta-visited size-easing and cook meta-visited and cook meta-visited and cook m |
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| according to disk that may be used according to these assays are publicly available (e.g., through the ATCCP) and and or may be tourishing spectrated. Exemplanty cells that may be used according to these assays include microvascular endothelial cells (MYEC).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Addition of Kinnes usay, Kinnes usays, Inc. Signaling Pathway  RK signal transduction that regulate call polification of including anti-foliation are well known in the art and may be used or outside modified to assess the ability of polypeptides of the invention (including anti-foliation and agoints or unagoniss or unagoniss or unagoniss, or unagoniss, or unagoniss, or the polification, advisation, and affectation, and infercentation, the ERK kinnes, activation, and affectation, and interchangion for rounsies by monticed to use BK kinnes, and the invention in including anti-foliated to see BK kinnes, and the invention in clud-bring anti-foliated to see BK kinnes, and agoniss or antiquents of the invention of including anti-foliated to see BK (Fig. 110).  (1998), Le Marchand-Bussel Y. Exp. (1998), Kraists, IM, Brobern Sc. 6799), Kraists, IM, Brobern Sc. 6799, He invention of the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLWBKOS 533 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 139                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|  | incomorated by reference in its        | described helow under                  |
|--|----------------------------------------|----------------------------------------|
|  | entirety Mouse adinocyte cells that    | "Hynemroliferative Disorders")         |
|  | may be used according to these         | Preferred indications include blood    |
|  | assays are publicly available (e.g.,   | disorders (e.g., hypertension,         |
|  | through the ATCCTM). Exemplary         | congestive heart failure, blood vessel |
|  | mouse adipocyte cells that may be      | blockage, heart disease, stroke,       |
|  | used according to these assays         | impotence and/or as described below    |
|  | include 3T3-L1 cells. 3T3-L1 is an     | under "Immune Activity",               |
|  | adherent mouse preadipocyte cell       | "Cardiovascular Disorders", and/or     |
|  | line that is a continuous substrain of | "Blood-Related Disorders"), immune     |
|  | 3T3 fibroblast cells developed         | disorders (e.g., as described below    |
|  | through clonal isolation and undergo   | under "Immune Activity"), neural       |
|  | a pre-adipocyte to adipose-like        | disorders (e.g., as described below    |
|  | conversion under appropriate           | under "Neural Activity and             |
|  | differentiation conditions known in    | Neurological Diseases"), and           |
|  | the art.                               | infection (e.g., as described below    |
|  |                                        | under "Infectious Disease").           |
|  |                                        | A highly preferred indication is       |
|  |                                        | diabetes mellitus. An additional       |
|  |                                        | highly preferred indication is a       |
|  |                                        | complication associated with           |
|  |                                        | diabetes (e.g., diabetic retinopathy,  |
|  |                                        | diabetic nephropathy, kidney disease   |
|  |                                        | (e.g., renal failure, nephropathy      |
|  |                                        | and/or other diseases and disorders as |
|  |                                        | described in the "Renal Disorders"     |
|  |                                        | section below), diabetic neuropathy,   |
|  |                                        | nerve disease and nerve damage         |
|  |                                        | (e.g., due to diabetic neuropathy),    |
|  |                                        | blood vessel blockage, heart disease,  |
|  |                                        | stroke, impotence (e.g., due to        |
|  |                                        | diabetic neuropathy or blood vessel    |
|  |                                        | blockage), seizures, mental            |
|  |                                        | confusion, drowsiness, nonketotic      |
|  |                                        | hyperglycemic-hyperosmolar coma,       |
|  |                                        | cardiovascular disease (e.g., heart    |
|  |                                        | disease, atherosclerosis,              |

| reputpora, ledgeriai and breast, colon, and kidney cancer. Additional preferred indications include and and additional posterior, lung partents, lung partents, cooplageal, stometh, luver, and unimary cancer. Highly preferred indications include brighty referred indications, such as of pre-morphistic conditions, such as, for analytic dysplasia. | A preferred anotherine to rithe invention includes a method for includes a method for includes a method for allowing (e.g., tucnessing) TNF alpha production. Preferred indecations includes a method for stimulating (e.g., increasing) TNF alpha obsolution. Develored indecations includes hood disorders (e.g., as excepted hold-entered indecations include blood disorders (e.g., as blood-Related Disorders, and off-or Candiovascular Disorders, and off-or Candiovascular Disorders, and off-or Candiovascular Disorders, and off-or candiovascular Disorders, and confusions of the production include autoimmune diseases (e.g., theamsoid arthritis, systemic lupus eryttemaosis and or as described below), boosting a Teel1-mediated immune response, and suppressing a Teel1-mediated dispense and suppressing a Teel1-mediated diseases.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | treassary find the activation of treassary find the activation of treassary find the art and may be used to require the art and may be used to routinely modified to assess the ability of polypeptides of the invention (including anthodies and applied to a polyperidise of the invention (including anthodies and invention) to regulate the seature invention) to regulate the seature invention) to regulate the seature invention) to regulate the seature expression of genes involved in invention) to regulate the seature expression of genes involved in expression of genes involved in the researchion through the SRE that the activity of the polypeptides of the invention (including antipodies of the invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in invention) include assays disclosed in the invention of the assays disclosed in the activity of the polyperides.  Henthorn et al. Proc Natl Acad Sci (1993), Albert and Acad Sci (1993), Armed Sci (1994), Arm |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Advancion of transcription through a man-response element in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 534                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HLWBY76                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 95                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| 111   | 117 (1997), the content of each of      | inflammation and inflammatory          |
|-------|-----------------------------------------|----------------------------------------|
| whi   | which are herein incorporated by        | disorders, and treating joint damage   |
| aja.  | reference in its entirety. T cells that | in patients with rheumatoid arthritis. |
| may   | may be used according to these          | An additional highly preferred         |
| assa  | assays are publicly available (e.g.,    | indication is sepsis. Highly           |
| thro  | through the ATCCTM). Exemplary          | preferred indications include          |
| nom   | mouse T cells that may be used          | neoplastic diseases (e.g., leukemia,   |
| acci  | according to these assays include the   | lymphoma, and/or as described          |
| E     | CTLL cell line, which is an IL-2        | below under "Hyperproliferative        |
| deb   | dependent suspension culture of T       | Disorders"). Additionally, highly      |
| celli | cells with cytotoxic activity.          | preferred indications include          |
|       |                                         | neoplasms and cancers, such as, for    |
|       |                                         | example, leukemia, lymphoma,           |
|       |                                         | melanoma, glioma (e.g., malignant      |
|       |                                         | glioma), solid tumors, and prostate,   |
|       |                                         | breast, lung, colon, pancreatic,       |
|       |                                         | esophageal, stomach, brain, liver and  |
|       |                                         | urinary cancer. Other preferred        |
|       |                                         | indications include benign             |
|       |                                         | dysproliferative disorders and pre-    |
|       |                                         | neoplastic conditions, such as, for    |
|       |                                         | example, hyperplasia, metaplasia,      |
|       |                                         | and/or dysplasia. Preferred            |
|       |                                         | indications include anemia,            |
|       |                                         | pancytopenia, leukopenia,              |
|       |                                         | thrombocytopenia, Hodgkin's            |
|       |                                         | disease, acute lymphocytic anemia      |
|       |                                         | (ALL), plasmacytomas, multiple         |
|       |                                         | myeloma, Burkitt's lymphoma,           |
|       |                                         | arthritis, AIDS, granulomatous         |
|       |                                         | disease, inflammatory bowel disease,   |
|       |                                         | neutropenia, neutrophilia, psoriasis,  |
|       |                                         | suppression of immune reactions to     |
|       |                                         | transplanted organs and tissues,       |
|       |                                         | hemophilia, hypercoagulation,          |
|       |                                         | diabetes mellitus, endocarditis,       |
|       |                                         | meningitis, Lyme Disease, cardiac      |

|                |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III.W.CP05 535 | Adjough Bathway Signalling Pathway | ceample an GSK-3 usays, for PIR threas essays, for PIR threas eighal threats usays, for PIR threas eighal threatherien that ergalate glatoses metabolism and cell arreptate glatoses metabolism and cell arreptate glatoses metabolism and cell and threatheries and threatheries and threatheries and threatheries and gonism and threatheries are admitted to seasons the ability of polypeptides of the invention) to promote or infilted glatoses (including anthodies and gonisis or appeared and arreptate of the arrest of the present of the arrest of the present of the arrest of the | A highly preficied enhabilment of the invention includes a method for including a discount includes a method for including a discount includes a method for invention includes a method for decreasing enhabitors and a proper comparing the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the propertie |

| ii. | include 3T3-L1 cells. 3T3-L1 is an    | impotence and/or as described below    |
|-----|---------------------------------------|----------------------------------------|
| ac  | adherent mouse preadipocyte cell      | under "Immune Activity",               |
|     | line that is a continous substrain of | "Cardiovascular Disorders", and/or     |
| - A | 3T3 fibroblast cells developed        | "Blood-Related Disorders"), immune     |
| #   | through clonal isolation and undergo  | disorders (e.g., as described below    |
| e   | a pre-adipocyte to adipose-like       | under "Immune Activity"), neural       |
|     | conversion under appropriate          | disorders (e.g., as described below    |
| -5  | differentiation conditions known in   | under "Neural Activity and             |
| -   | the art.                              | Neurological Diseases"), and           |
|     |                                       | infection (e.g., as described below    |
|     |                                       | under "Infectious Disease"). A         |
|     |                                       | highly preferred indication is         |
|     |                                       | diabetes mellitus. An                  |
|     |                                       | additional highly preferred indication |
|     |                                       | is a complication associated with      |
|     |                                       | diabetes (e.g., diabetic retinopathy,  |
|     |                                       | diabetic nephropathy, kidney disease   |
|     |                                       | (e.g., renal failure, nephropathy      |
|     |                                       | and/or other diseases and disorders as |
|     |                                       | described in the "Renal Disorders"     |
|     |                                       | section below), diabetic neuropathy,   |
|     |                                       | nerve disease and nerve damage (e.g.,  |
|     |                                       | due to diabetic neuropathy), blood     |
|     |                                       | vessel blockage, heart disease,        |
|     |                                       | stroke, impotence (e.g., due to        |
|     |                                       | diabetic neuropathy or blood vessel    |
|     |                                       | blockage), seizures, mental            |
|     |                                       | confusion, drowsiness, nonketotic      |
|     |                                       | hyperglycemic-hyperosmolar coma,       |
|     |                                       | cardiovascular disease (e.g., heart    |
|     |                                       | disease, atherosclerosis,              |
|     |                                       | microvascular disease, hypertension,   |
|     |                                       | stroke, and other diseases and         |
|     |                                       | disorders as described in the          |
|     |                                       | "Cardiovascular Disorders" section     |
|     |                                       | below), dyslipidemia, endocrine        |
|     |                                       | disorders (as described in the         |

|  |  | "Endocrine Disorders" section           |
|--|--|-----------------------------------------|
|  |  | halour) nauronathy vicion               |
|  |  | inneimont (e.g. disherio metinomethr    |
|  |  | impaintent (c.g., dianeur remopant)     |
|  |  | and blindness), ulcers and impaired     |
|  |  | wound healing, infection (e.g.,         |
|  |  | infectious diseases and disorders as    |
|  |  | described in the "Infectious            |
|  |  | Diseases" section below, especially     |
|  |  | of the urinary tract and skin), carpal  |
|  |  | tunnel syndrome and Dupuytren's         |
|  |  | contracture). An additional             |
|  |  | highly preferred indication is obesity  |
|  |  | and/or complications associated with    |
|  |  | obesity. Additional highly preferred    |
|  |  | indications include weight loss or      |
|  |  | alternatively, weight gain.             |
|  |  | Additional highly preferred             |
|  |  | indications are complications           |
|  |  | associated with insulin resistance.     |
|  |  | Additional highly preferred             |
|  |  | indications are disorders of the        |
|  |  | musculoskeletal systems including       |
|  |  | myopathies, muscular dystrophy,         |
|  |  | and/or as described herein.             |
|  |  | Additional highly preferred             |
|  |  | indications include, hypertension,      |
|  |  | coronary artery disease,                |
|  |  | dyslipidemia, gallstones,               |
|  |  | osteoarthritis, degenerative arthritis, |
|  |  | eating disorders, fibrosis, cachexia,   |
|  |  | and kidney diseases or disorders.       |
|  |  | Highly preferred indications include    |
|  |  | neoplasms and cancer, such as,          |
|  |  | lipoma, liposarcoma, lymphoma,          |
|  |  | leukemia and breast, colon, and         |
|  |  | kidney cancer. Additional highly        |
|  |  | preferred indications include           |

| medanona, prostate, lung, propuente, lung, propuente, seopulgael, sommeh, brain, liver, and unimy cancer. Other preferred indications include benign dyspotilierative disorders and pre-neoplassic contitions, saidt as, pre-neoplassic contitions, saidt as, and de ceample, hyperplassin, metaplassia, and/or dyspotissia, metaplassia, and/or dyspotissia. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                               | Kinnes ensay. NIK Kinnes ensays for a Kinnes ensays for a problematic problematic activation, activation, activation, activation, activation, activation of a season and any be used or roll number to make the ability of polyperidics of the invention (including antibodies and invention) to promote or inhibit cell invention) to promote or inhibit cell invention) to promote or inhibit cell invention) to promote or inhibit cell invention) to promote or inhibit cell invention) to promote or inhibit cell invention and apoptosis. Exemplar usays for the invention DNK kinase-induced activity of the invention of including antibodies and agonisis or autagoniss of the invention include the assays disclosed in Forner et al. (1992) Expirates IM Biochem See Symp 64:29-48 (1098); Chang and Kern Naure 410(6824);37-40(2001); and Cobb MII, Prog Biophys Mob Bioly in contents of each of which are herein its senties. |
|                                                                                                                                                                                                                                                                                                                                                               | Activation of JNK Signaling Pathway in Signaling Pathway in immune cols (such as cosinophils).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                               | 585                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                               | 131 HLWCF05                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| be used according to these assays | include cosmopinus, cosmopinus are<br>important in the late stage of allergic | reactions; they are recruited to tissues | and mediate the inflammatory | response of late stage allergic | reaction. Moreover, exemplary | assays that may be used or routinely | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to | modulate signal transduction, cell | proliferation, activation, or apoptosis | in eosinophils include assays | disclosed and/or cited in: Zhang JP, | et al., "Role of caspases in | dexamethasone-induced apoptosis | and activation of c-Jun NH2-terminal | kinase and p38 mitogen-activated | protein kinase in human cosinophils" | Clin Exp Immunol; Oct;122(1):20-7 | (2000); Hebestreit H, et al., | "Disruption of fas receptor signaling | by nitric oxide in eosinophils" J Exp | Med; Feb 2;187(3):415-25 (1998); J | Allergy Clin Immunol 1999 | Sep;104(3 Pt 1):565-74; and, Sousa | AR, et al., "In vivo resistance to | corticosteroids in bronchial asthma is | associated with enhanced | phosyphorylation of JUN N-terminal | kinase and failure of prednisolone to | inhibit JUN N-terminal kinase | phosphorylation" J Allergy Clin | Immunol; Sep;104(3 Pt 1):565-74 | (1999); the contents of each of which |
|-----------------------------------|-------------------------------------------------------------------------------|------------------------------------------|------------------------------|---------------------------------|-------------------------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|----------------------------------|------------------------------------|-----------------------------------------|-------------------------------|--------------------------------------|------------------------------|---------------------------------|--------------------------------------|----------------------------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------|------------------------------------|------------------------------------|----------------------------------------|--------------------------|------------------------------------|---------------------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------------|
|                                   |                                                                               |                                          |                              |                                 |                               |                                      |                                   |                               |                                       |                                  |                                    |                                         |                               |                                      |                              |                                 |                                      |                                  |                                      |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          |                                    |                                       |                               |                                 |                                 |                                       |
| _                                 |                                                                               |                                          |                              |                                 |                               |                                      |                                   |                               |                                       |                                  |                                    |                                         |                               |                                      |                              |                                 |                                      |                                  |                                      |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          |                                    |                                       |                               |                                 |                                 |                                       |

|                                                       | Preferred indications include | neoplastic diseases (e.g., as described | below under "Hyperproliferative    | Disorders"), blood disorders (e.g., as | described below under "Immune | Activity", "Cardiovascular | Disorders", and/or "Blood-Related | Disorders"), and infection (e.g., an | infectious disease as described below | under "Infectious Disease"). Highly | preferred indications include | autoimmune diseases (e.g.,           | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below) and | immunodeficiencies (e.g., as          | described below). Additional highly   | preferred indications include | inflammation and inflammatory | lisorders. Highly preferred | ndications also include neoplastic | discases (e.g., leukemia, lymphoma, | and/or as described below under | 'Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as, | eukemia, lymphoma, prostate, | preast, lung, colon, pancreatic,          | esophageal, stomach, brain, liver,   | and urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia,<br>and/or dvenlasia Preferred |
|-------------------------------------------------------|-------------------------------|-----------------------------------------|------------------------------------|----------------------------------------|-------------------------------|----------------------------|-----------------------------------|--------------------------------------|---------------------------------------|-------------------------------------|-------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|-------------------------------|-------------------------------|-----------------------------|------------------------------------|-------------------------------------|---------------------------------|----------------------------------|--------------------------------------|---------------------------------|------------------------------|-------------------------------------------|--------------------------------------|-------------------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------------------------------------------------------------|
| are herein incorporated by reference in its entirety. | Assays for the activation of  | transcription through the AP1           | response element are well-known in | the art and may be used or routinely   | Jo                            | _                          | sts or                            | antagonists of the invention) to     | modulate growth and other cell        | -                                   | transcription through the AP1 | response element that may be used or | routinely modified to test AP1-      | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | _                             | i and                         | Ť                           |                                    | Ť                                   |                                 | . (1661)                         | Chang et al., Mol Cell Biol          | _                               | _                            | (1999), the contents of each of which   1 | are herein incorporated by reference | in its entirety. Human T cells that |                            |                                     | ary                                 | human T cells that may be used                                  |
|                                                       | Activation of                 | transcription through                   | AP1 response element               | in immune cells (such                  | as T-cells).                  |                            |                                   |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                               |                               |                             |                                    |                                     |                                 |                                  |                                      |                                 |                              |                                           |                                      |                                     |                            |                                     |                                     |                                                                 |
|                                                       | 535                           |                                         |                                    |                                        |                               |                            |                                   |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                               |                               |                             |                                    |                                     |                                 |                                  |                                      |                                 |                              |                                           |                                      |                                     |                            |                                     |                                     |                                                                 |
|                                                       | HLWCF05                       |                                         |                                    |                                        |                               |                            |                                   |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                               |                               |                             |                                    |                                     |                                 |                                  |                                      |                                 |                              |                                           |                                      |                                     |                            |                                     |                                     |                                                                 |
|                                                       |                               | 131                                     |                                    |                                        |                               |                            |                                   |                                      |                                       |                                     |                               |                                      |                                      |                                   |                                |                                       |                                       |                               |                               |                             |                                    |                                     |                                 |                                  |                                      |                                 |                              |                                           |                                      |                                     |                            |                                     |                                     |                                                                 |

| IL-2 and indications include arthritis, asthma, culture AIDTS, alleggs, arenia, pancyopenia, lethopenia, thrombocytopenia, thrombocytopenia, thrombocytopenia, thrombocytopenia, thrombocytopenia, thrombocytopenia, thrombocytopenia (AIDT), plastneytomas, multiple myeloma, plantiti's bymphom, aminiple myeloma, Burkit's bymphom, paraphrosation of immune reactions to transplanted organs and this sections to transplanted organs and this sections to transplanted organs and this sections to transplanted meninglist, and tyme Diseases. | A highly perfered enhodiment  28 of the invention includes a nethod  outnierly constrained a cell proliferation.  An alternative highly preferred candon and on some or constrained and alternative highly preferred and proliferation includes a method for includes a method for inhibiting I professed in the constraint of the invention includes a method for antiquion preferred embedianent of the properties of the includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for antiquion includes a method for alternation includes a method inflammatory altharmation inflammatory and inflammatory distances. Highly preferred adisorders. Highly preferred disorders. |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Assays for the activation of Sassays and may be used or routinely modified to assess the ability of polypeptides of the invention of polypeptides of the invention of polypeptides of the invention of polypeptides of the invention of autgenties of the invention of autgenties of the invention of autgenties of the invention of the invention of the invention of the invention of the invention of including authorities and agonists or autgenties of the invention of including authorities and agonists or autgenties of the invention of including authorities of the invention of including authorities of the invention include usays disclosed in Bargard at al. Gene 66-14 (1998). Utilen and Matha. Methods in Engypand 216-23-264 (1998). Meditine and lanchelli, Jimmunol 166(49). 2477-2481.                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Advancing Advancing transcription through CO28 response element in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 131 HLWGF05                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| (2001); and Butscher et al., J Biol           | indications include autoimmune         |
|-----------------------------------------------|----------------------------------------|
| Chem 3(1):552-560 (1998), the                 | diseases (e.g., rheumatoid arthritis,  |
| contents of each of which are herein          | systemic lupus erythematosis,          |
| incorporated by reference in its              | multiple sclerosis and/or as described |
| entirety. T cells that may be used            | below), immunodeficiencies (e.g., as   |
| according to these assays are publicly        | described below), boosting a T cell-   |
| available (e.g., through the                  | mediated immune response, and          |
| ATCC <sup>TM</sup> ). Exemplary human T cells | suppressing a T cell-mediated          |
| that may be used according to these           | immune response. Highly                |
| assays include the SUPT cell line,            | preferred indications include          |
| which is a suspension culture of IL-2         | neoplastic diseases (e.g., melanoma,   |
| and IL-4 responsive T cells.                  | renal cell carcinoma, leukemia,        |
|                                               | lymphoma, and/or as described          |
|                                               | below under "Hyperproliferative        |
|                                               | Disorders"). Highly preferred          |
|                                               | indications include neoplasms and      |
|                                               | cancers, such as, for example,         |
|                                               | melanoma (e.g., metastatic             |
|                                               | melanoma), renal cell carcinoma        |
|                                               | (e.g., metastatic renal cell           |
|                                               | carcinoma), leukemia, lymphoma         |
|                                               | (e.g., T cell lymphoma), and prostate, |
|                                               | breast, lung, colon, pancreatic,       |
|                                               | esophageal, stomach, brain, liver and  |
|                                               | urinary cancer. Other preferred        |
|                                               | indications include benign             |
|                                               | dysproliferative disorders and pre-    |
|                                               | neoplastic conditions, such as, for    |
|                                               | example, hyperplasia, metaplasia,      |
|                                               | and/or dysplasia. A highly             |
|                                               | preferred indication includes          |
|                                               | infection (e.g., AIDS, tuberculosis,   |
|                                               | infections associated with             |
|                                               | granulomatous disease, and             |
|                                               | osteoporosis, and/or as described      |
|                                               | below under "Infectious Disease").     |
|                                               | A highly preferred indication is       |

| MDB. Additional highly preferred indications include suppression of indications include suppression of mammer reactions to transplanted organs and/or its states, workink; personals, and/or its states, workink; personals, and/or its states, workink; personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, personals, pers | the Nuclear include blood disorders (e.g., ss. vertherown in each of how under 'Immune Austring,'' Blood-Related to the work of the search of how under 'Immune Austring,'' Blood-Related to the search of the work of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search of the search |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of Assays for the activation of Termscription through the Nuclear NR-AT response Factor of Activated Teelin (NR-AT) element in immune response character are well-known in cells (such as T-cells). The art and may be used or routinely modified to assess the ability of polypophics of the invention (including anabodies and agoniss or anaponiss of the invention in egaliate NR-AT transcription factors involved in immunomodiation.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 53.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLWCP0S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 131                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infection diseases). Below under "Infectious Diseases").                                                                                                                                   | repetred indications inclined in prepared indications inclined in prophenical diseases (e.g., letkernid, below under "Hyperprolificative below under "Hyperprolificative below under "Hyperprolificative inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined inclined |
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| response element that may be used or routinely modified to test NFAT- response element activity of  polypeptides of the invention  (including antibodies and agonists or  anagonists of the rurention include  anagonists of the rurention bicklete   Main, Methods in Enzymol  Main, Methods in Enzymol  Pics 32-586 (1993); Henthom et al., Proc Mail Acad Sci USA 85:632-  Proc Mail Acad Sci USA 85:632-  Biodyrs Acat 1980; Il-1 Biodnim  Biophys Acat 1980; Il-1 Biodnim  Biodyrs Acat 1980; Il-1 Biodnim  Biodyrs Acat 1980; Il-1 Biodnim  Biod 31(10):1221-1236 (1993);  Proces et al., Ent Immunol  29(3):538-84(1999); and Yessen et al., Thiol Chem 268(19); 1428-  1929; (1993), in cometine of cachot which are herein incorporated by which are herein incorporated by which are herein incorporated by which are herein incorporated by which are herein incorporated by which are descenting to these says are publicly available (e.g., through the ATCCT <sup>3</sup> ). Exemplary  according to these sassys include the according to these sassys include the coll L-2 and IL-4 responsive T cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|     | HLWCF05 | 535 | Activation of            | Assays for the activation of            | Highly preferred indications          |
|-----|---------|-----|--------------------------|-----------------------------------------|---------------------------------------|
| 131 |         |     | transcription through    | transcription through the NFKB          | include inflammation and              |
|     |         |     | NFKB response            | response element are well-known in      | inflammatory disorders. Highly        |
|     |         |     | element in immune        | the art and may be used or routinely    | preferred indications include blood   |
|     |         |     | cells (such as T-cells). | modified to assess the ability of       | disorders (e.g., as described below   |
|     |         |     |                          | polypeptides of the invention           | under "Immune Activity", "Blood-      |
|     |         |     |                          | (including antibodies and agonists or   | Related Disorders", and/or            |
|     |         |     |                          | antagonists of the invention) to        | "Cardiovascular Disorders"). Highly   |
|     |         |     |                          | regulate NFKB transcription factors     | preferred indications include         |
|     |         |     |                          | and modulate expression of              | autoimmune diseases (e.g.,            |
|     |         |     |                          | immunomodulatory genes.                 | rheumatoid arthritis, systemic lupus  |
|     |         |     |                          | Exemplary assays for transcription      | erythematosis, multiple sclerosis     |
|     |         |     |                          | through the NFKB response element       | and/or as described below), and       |
|     |         |     |                          | that may be used or rountinely          | immunodeficiencies (e.g., as          |
|     |         |     |                          | modified to test NFKB-response          | described below). An additional       |
|     |         |     |                          | element activity of polypeptides of     | highly preferred indication is        |
|     |         |     |                          | the invention (including antibodies     | infection (e.g., AIDS, and/or an      |
|     |         |     |                          | and agonists or antagonists of the      | infectious disease as described below |
|     |         |     |                          | invention) include assays disclosed in  | under "Infectious Disease").          |
|     |         |     |                          | Berger et al., Gene 66:1-10 (1998);     | Highly preferred indications include  |
|     |         |     |                          | Cullen and Malm, Methods in             | neoplastic diseases (e.g., melanoma,  |
|     |         |     |                          | Enzymol 216:362-368 (1992);             | leukemia, lymphoma, and/or as         |
|     |         |     |                          | Henthorn et al., Proc Natl Acad Sci     | described below under                 |
|     |         |     |                          | USA 85:6342-6346 (1988); Black et       | "Hyperproliferative Disorders").      |
|     |         |     |                          | al., Virus Gnes 15(2):105-117           | Highly preferred indications include  |
|     |         |     |                          | (1997); and Fraser et al., 29(3):838-   | neoplasms and cancers, such           |
|     |         |     |                          | 844 (1999), the contents of each of     | as,melanoma, renal cell carcinoma,    |
|     |         |     |                          | which are herein incorporated by        | leukemia, lymphoma, and prostate,     |
|     |         |     |                          | reference in its entirety. T cells that | breast, lung, colon, pancreatic,      |
|     |         |     |                          | may be used according to these          | esophageal, stomach, brain, liver and |
|     |         |     |                          | assays are publicly available (e.g.,    | urinary cancer. Other preferred       |
|     |         |     |                          | through the ATCCTM). Exemplary          | indications include benign            |
|     |         |     |                          | human T cells that may be used          | dysproliferative disorders and pre-   |
|     |         |     |                          | according to these assays include the   | neoplastic conditions, such as, for   |
|     |         |     |                          | SUPT cell line, which is a suspension   | example, hyperplasia, metaplasia,     |
|     |         |     |                          | culture of IL-2 and IL-4 responsive T   | and/or dysplasia. Preferred           |
|     |         |     |                          | cells.                                  | indications also include anemia,      |

|     |         |     |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | throughous, landopenia, throughous, throughous, and throughous, and purpoyeria, Indegin's sides, acute bymphocytic among (ALL), plasmacytonia, multiple declaration, and the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the proposal grant of the pro |
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| 132 | HLYAC95 | 336 | Production of Production of edis | registration of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics and may be used or the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the physics of the | A highly prefixed embodiment of the invention includes a method for standing the production of HPAE, An alternative tripling preferred embodiment of the invention of ministring the production of full facilities a method for ministring the production of 1PAE, and the method of ministring the production of 1PAE, and the production of 1PAE, and the production of 1PAE, and the production of 1PAE, and the production of 1PAE, and the production is ministriction, as accinited below the change of the production as sociated with chronic granulomators to diseased, "Highly preferred indications include a morphism and or as described below under "Infections described below under "Infections associated with chronic granulomators disease and production of the preferred indications include autoimmune disease (e.g., the unity set of the action of the second of the described help of the preferred indications include autoimmune disease (e.g., the unity set of the action of second of se second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of second of sec |

|   |                                        | 11.44. 11. 11. 11. 11. 11. 11. 11. 11. 1 | J                                                                  |
|---|----------------------------------------|------------------------------------------|--------------------------------------------------------------------|
| _ | III III III III III III III III III II | United of Centurated                     | described below), boosting a 1 cen-                                |
|   | Immumity<br>foot for in                | immunity. Exemplarly assays that         | mediated innume response, and                                      |
|   | evaluate t                             | exalinate the production of extokines    | immine response Additional highly                                  |
|   | such as In                             | cuch as Interferon gamma (IFNg)          | minume response. Accuronal inging<br>preferred indications include |
|   | and the ac                             | and the activation of T cells. Such      | inflammation and inflammatory                                      |
|   | assays tha                             | assays that may be used or routinely     | disorders. Additional preferred                                    |
|   | modified                               | modified to test immunomodulatory        | indications include idiopathic                                     |
|   | activity of                            | activity of polypeptides of the          | pulmonary fibrosis. Highly                                         |
|   | invention                              | invention (including antibodies and      | preferred indications include                                      |
|   | agonists o                             | agonists or antagonists of the           | neoplastic diseases (e.g., leukemia,                               |
|   | invention                              | invention) include the assays            | lymphoma, melanoma, and/or as                                      |
|   | disclosed                              | disclosed in Miraglia et al., J          | described below under                                              |
|   | Biomolec                               | Biomolecular Screening 4:193-204         | "Hyperproliferative Disorders").                                   |
|   | (1999); R                              | (1999); Rowland et al.,                  | Highly preferred indications include                               |
|   | "Lympho                                | "Lymphocytes: a practical approach"      | neoplasms and cancers, such as, for                                |
|   | Chapter 6                              | Chapter 6:138-160 (2000); Gonzalez       | example, lcukemia, lymphoma,                                       |
|   | et al., J Cl                           | et al., J Clin Lab Anal 8(5):225-233     | melanoma, and prostate, breast, lung,                              |
|   | (1995); B                              | (1995); Billiau et al., Ann NY Acad      | colon, pancreatic, esophageal,                                     |
|   | Sci 856:2                              | Sci 856:22-32 (1998); Boehm et al.,      | stomach, brain, liver and urinary                                  |
|   | Annu Rev                               | Annu Rev Immunol 15:749-795              | cancer. Other preferred indications                                |
|   | (1997), ar                             | (1997), and Rheumatology (Oxford)        | include benign dysproliferative                                    |
|   | 38(3):214                              | 38(3):214-20 (1999), the contents of     | disorders and pre-neoplastic                                       |
|   | each of w                              | each of which are herein                 | conditions, such as, for example,                                  |
|   | incorpora                              | incorporated by reference in its         | hyperplasia, metaplasia, and/or                                    |
|   | entirety.                              | entirety. Human T cells that may be      | dysplasia. Preferred indications                                   |
|   | nsed acco                              | used according to these assays may       | include anemia, pancytopenia,                                      |
|   | be isolate                             | be isolated using techniques             | leukopenia, thrombocytopenia,                                      |
|   | disclosed                              | disclosed herein or otherwise known      | Hodgkin's disease, acute                                           |
|   | in the art.                            | in the art. Human T cells are primary    | lymphocytic anemia (ALL),                                          |
|   | human lyı                              | human lymphocytes that mature in         | plasmacytomas, multiple myeloma,                                   |
|   | the thymn                              | the thymus and express a T Cell          | Burkitt's lymphoma, arthritis, AIDS,                               |
|   | receptor a                             | receptor and CD3, CD4, or CD8.           | granulomatous disease, inflammatory                                |
|   | These cell                             | These cells mediate humoral or cell-     | bowel disease, sepsis, neutropenia,                                |
|   | mediated                               | mediated immunity and may be             | neutrophilia, psoriasis, suppression                               |
|   | preactivat                             | preactivated to enhance                  | of immune reactions to transplanted                                |
|   | responsiveness to                      | eness to                                 | organs and tissues, hemophilia,                                    |
|   |                                        |                                          |                                                                    |

|     |         |     |                                          | immunomodulatory factors.                                                  | hypercoagulation, diabetes mellius,<br>endocarditis, meningitis, Lyme<br>Disease, asthma and allergy. |
|-----|---------|-----|------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| 132 | HLYAC95 | 536 | Stimulation of insulin<br>secretion from | Assays for measuring secretion of<br>insulin are well-known in the art and | A highly preferred indication is<br>diabetes mellitus. An                                             |
|     |         |     | pancreatic beta cells.                   | may be used or routinely modified to                                       | additional highly preferred indication                                                                |
|     |         |     |                                          | assess the ability of polypeptides of                                      | is a complication associated with                                                                     |
|     |         |     |                                          | the invention (including antibodies                                        | diabetes (e.g., diabetic retinopathy,                                                                 |
|     |         |     |                                          | and agonists or antagonists of the                                         | diabetic nephropathy, kidney disease                                                                  |
|     |         |     |                                          | secretion. For example, insulin                                            | and/or other diseases and disorders as                                                                |
|     |         |     |                                          | secretion is measured by FMAT                                              | described in the "Renal Disorders"                                                                    |
|     |         |     |                                          | using anti-rat insulin antibodics.                                         | section below), diabetic neuropathy,                                                                  |
|     |         |     |                                          | Insulin secretion from pancreatic beta                                     | nerve disease and nerve damage                                                                        |
|     |         |     |                                          | cells is upregulated by glucose and                                        | (e.g., due to diabetic neuropathy),                                                                   |
|     |         |     |                                          | also by certain proteins/peptides, and                                     | blood vessel blockage, heart disease,                                                                 |
|     |         |     |                                          | disregulation is a key component in                                        | stroke, impotence (e.g., due to                                                                       |
|     |         |     |                                          | diabetes. Exemplary assays that may                                        | diabetic neuropathy or blood vessel                                                                   |
|     |         |     |                                          | be used or routinely modified to test                                      | blockage), seizures, mental                                                                           |
|     |         |     |                                          | for stimulation of insulin secretion                                       | confusion, drowsiness, nonketotic                                                                     |
|     |         |     |                                          | (from pancreatic cells) by                                                 | hyperglycemic-hyperosmolar coma,                                                                      |
|     |         |     |                                          | polypeptides of the invention                                              | cardiovascular disease (e.g., heart                                                                   |
|     |         |     |                                          | (including antibodics and agonists or                                      | discase, atherosclerosis,                                                                             |
|     |         |     |                                          | antagonists of the invention) include                                      | microvascular disease, hypertension,                                                                  |
|     |         |     |                                          | assays disclosed in: Ahren, B., et al.,                                    | stroke, and other diseases and                                                                        |
|     |         |     |                                          | Am J Physiol, 277(4 Pt 2):R959-66                                          | disorders as described in the                                                                         |
|     |         |     |                                          | (1999); Li, M., et al., Endocrinology,                                     | "Cardiovascular Disorders" section                                                                    |
|     |         |     |                                          | 138(9):3735-40 (1997); Kim, K.H.,                                          | below), dyslipidemia, endocrine                                                                       |
|     |         |     |                                          | et al., PEBS Lett, 51/(2):25/-9                                            | disorders (as described in the                                                                        |
|     |         |     |                                          | (1995); and, Miraglia S et. al.,                                           | "Endocrine Disorders" section                                                                         |
|     |         |     |                                          | Journal of Biomolecular Screening,                                         | below), neuropathy, vision                                                                            |
|     |         |     |                                          | 4:193-204 (1999), the contents of                                          | impairment (e.g., diabetic retinopathy                                                                |
|     |         |     |                                          | each of which is herein incorporated                                       | and blindness), ulcers and impaired                                                                   |
|     |         |     |                                          | by reference in its entirety.                                              | wound healing, and infection (e.g.,                                                                   |
|     |         |     |                                          | Pancreatic cells that may be used                                          | infectious diseases and disorders as                                                                  |
|     |         |     |                                          | according to these assays are publicly                                     | described in the "Infectious                                                                          |
|     |         |     |                                          | available (e.g., unough the ATCC)                                          | Diseases section below, especially                                                                    |

| HLYAN59 | 537 | Production of VCAM                                                                           | Percentage of particular and an open area asserting the according to these asserts much an Intelligent and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a service and a servi | contracture) and hypotyteris's contracture).  An additional industrial and additional industrial and additional industrial and one of the contracture is second and industrial industrial highly preferred industrial highly preferred industrial highly preferred industrial highly preferred industrial highly preferred industrial and industrial highly preferred industrial with institutions associated with insulin resistance.  Highly preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------|-----|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | Ī   | in croductical cells (such as human urabilical voin cuchbical voin cuchbical cells ((HIVEC)) | CACAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention frieduling antibodies and agonists or antiponists of the invention for the properties of the remember of the construction to regulation (VAM) to the copression of consume the uprogulation of cell surface VAM-1 expression or to conduct like the included by the consumer the uprogulation of cell surface VAM-1 expression or conducting that time uprogulation of cell surface VAM-1 expression or conducting that time influencions that include, but are not illumication suggestionsis, vascular permeability, vascular route, and intender that include, but are not illumined on aggorgenesis, vascular permeability, vascular route, and included in cells that run permeability vascular included in the sassists include thrama unbilicial vein reactions of VCAM are available from commercial are available from commercial are available from commercial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | information (extern and retroits).  The information (extern and retroits).  All alreys Highly preferred indications and alreys. Highly preferred indications include information and information discorders, considerable and another sections of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the |

|    |         |     |                                  | protein, can be upregulated by optokines or other factors, and countributes to the extervesation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoving immune and mildmandory responses.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | cvample, lyperplasia, metaplasia,<br>and/or dysplasia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----|---------|-----|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 34 | HLYAP91 | 258 | Adjoyoyte ERK<br>Sigming Pathway | coumple an Elle Linnes assays, for relations assays, for the Res again transpared to the trapplant cell position and the Linnes assays, for the Res again transpared to the trapplant cell position of differentiation are veal Loowen in the sat and may be used or routinely modified to assass the ability of polypeptides of the against or of the ability of polypeptides of the against or transpared so that against or transpared so the ability of polypeptides of the proliferation, activation, and recently of the proliferation, activation, and recently of the proliferation, activation, and recently of RK kinass activity that may be used the RK kinass activity that may be used RK kinass activity that may be used the RK kinass activity that may be used the RK kinass activity that may be used the Change of the invention include the invention include the invention include the assays disclosed in Forter et al. (1998); Le Manchand-Brasel Y. Exp. [107,115-12] (1999); Kyrickie JM Biochem Soc Sym 64,29-48 (1999); Clanchound Diabetess 11 (1998); Le Manchand-Brasel V. Exp. [107,115-12] (1999); Kyrickie JM JM Long Biochem Soc Sym 64,29-48 (1999); the contents of 41,487-500 (1999); the contents of 41,487-500 (1999); the contents of | A highty preferred enhabition of the invention includes a method for stimilating adjocycyc proliferation. An alternative highty proferred enhabition of an alternative highty proferred enhabition of the invention includes a method for inhibiting adjocycyc proliferation. A highty preferred enhabitiment of the invention includes a method for inhibiting adjocycyc proferration. A highly preferred enhabitiment of the invention includes a method for inhibiting and adjocyce differentiation. A failuppen preferred enhabitiment of the invention includes a method for inhibiting and adjocyce differentiation. A highly preferred enhabitiment of the invention includes a method for simulating (e.g., increasing) and adjocyce differentiation. A highly preferred embodiment of the invention in highly preferred embodiment of the invention in all depress a method for inhibiting the activation of (e.g., accessing) and or intertvating deservations in caretvating dissorters (e.g., as described below mide.* Takociric Discoders*). Highly preferred indications is lab. michled indications as lab. michled indications as lab. |

|  | incomorated by reference in its        | described helow under                  |
|--|----------------------------------------|----------------------------------------|
|  | entirety. Mouse adinocyte cells that   | "Hyperproliferative Disorders").       |
|  | may be used according to these         | Preferred indications include blood    |
|  | assays are publicly available (e.g.,   | disorders (e.g., hypertension,         |
|  | through the ATCCTM). Exemplary         | congestive heart failure, blood vessel |
|  | mouse adipocyte cells that may be      | blockage, heart disease, stroke,       |
|  | used according to these assays         | impotence and/or as described below    |
|  | include 3T3-L1 cells. 3T3-L1 is an     | under "Immune Activity",               |
|  | adherent mouse preadipocyte cell       | "Cardiovascular Disorders", and/or     |
|  | line that is a continuous substrain of | "Blood-Related Disorders"), immune     |
|  | 3T3 fibroblast cells developed         | disorders (e.g., as described below    |
|  | through clonal isolation and undergo   | under "Immune Activity"), neural       |
|  | a pre-adipocyte to adipose-like        | disorders (e.g., as described below    |
|  | conversion under appropriate           | under "Neural Activity and             |
|  | differentiation conditions known in    | Neurological Diseases"), and           |
|  | the art.                               | infection (e.g., as described below    |
|  |                                        | under "Infectious Disease").           |
|  |                                        | A highly preferred indication is       |
|  |                                        | diabetes mellitus. An additional       |
|  |                                        | highly preferred indication is a       |
|  |                                        | complication associated with           |
|  |                                        | diabetes (e.g., diabetic retinopathy,  |
|  |                                        | diabetic nephropathy, kidney disease   |
|  |                                        | (e.g., renal failure, nephropathy      |
|  |                                        | and/or other diseases and disorders as |
|  |                                        | described in the "Renal Disorders"     |
|  |                                        | section below), diabetic neuropathy,   |
|  |                                        | nerve disease and nerve damage         |
|  |                                        | (e.g., due to diabetic neuropathy),    |
|  |                                        | blood vessel blockage, heart disease,  |
|  |                                        | stroke, impotence (e.g., due to        |
|  |                                        | diabetic neuropathy or blood vessel    |
|  |                                        | blockage), seizures, mental            |
|  |                                        | confusion, drowsiness, nonketotic      |
|  |                                        | hyperglycemic-hyperosmolar coma,       |
|  |                                        | cardiovascular disease (e.g., heart    |
|  |                                        | disease, atherosclerosis,              |

|  |  | microvascular disease hynertension      |
|--|--|-----------------------------------------|
|  |  | ottoolea and other discourse and        |
|  |  | stroke, and other diseases and          |
|  |  | disorders as described in the           |
|  |  | "Cardiovascular Disorders" section      |
|  |  | below), dyslipidemia, endocrine         |
|  |  | disorders (as described in the          |
|  |  | "Endocrine Disorders" section           |
|  |  | below), neuropathy, vision              |
|  |  | impairment (e.g., diabetic retinopathy  |
|  |  | and blindness), ulcers and impaired     |
|  |  | wound healing, infection (e.g.,         |
|  |  | infectious diseases and disorders as    |
|  |  | described in the "Infectious            |
|  |  | Diseases" section below (particularly   |
|  |  | of the urinary tract and skin). An      |
|  |  | additional highly preferred indication  |
|  |  | is obesity and/or complications         |
|  |  | associated with obesity. Additional     |
|  |  | highly preferred indications include    |
|  |  | weight loss or alternatively, weight    |
|  |  | gain. Additional highly                 |
|  |  | preferred indications are               |
|  |  | complications associated with insulin   |
|  |  | resistance. Additional highly           |
|  |  | preferred indications are disorders of  |
|  |  | the musculoskeletal systems             |
|  |  | including myopathies, muscular          |
|  |  | Š                                       |
|  |  | herein. Additional highly               |
|  |  | preferred indications include,          |
|  |  | hypertension, coronary artery           |
|  |  | disease, dyslipidemia, gallstones,      |
|  |  | osteoarthritis, degenerative arthritis, |
|  |  | eating disorders, fibrosis, cachexia,   |
|  |  | and kidney diseases or disorders.       |
|  |  | Preferred indications include           |
|  |  | neoplasms and cancer, such as,          |

| lymphoma, lenkernia and breast, oron, and sithey cuncer. Additional preferred indications include and externed indications include and and are members of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of th | A highly preferred embodimen of the invention includes a method for mecaning adaptive searched Andreasing adaptive searched and embodiment of the invention includes a method for decreasing adapsays earn'ral. A preferred methodiment of the invention includes a method for decreasing adapsays to politication. An alternative highly preferred methodiment of the invention includes a method for infinition alternative highly preferred methodiment of the invention includes a method for inhibiting adaptives profileration. A preferred embodiment of the invention includes a method for inhibiting adaptives to differentiation. An alternative highly preferred modificant of the invention includes a method for inhibiting adaptive differentiation. An alternative highly preferred modification for inhibiting adaptive differentiation. Highly preferred indications includes a method for inhibiting preferred indications include a fair roution includes a method for inhibiting preferred indications include a fair roution of indications include a fair roution of indications include a fair roution of indications include a fair roution of indications include a fair roution of indications include a fair roution of indications include a fair roution of indications include a fair fair roution of indications include a fair fair roution of indications include a fair roution of indications include a fair fair roution of indications include a fair fair roution include a fair fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fair roution in the fa                                                                                                                             |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Advivation of<br>Signalling Pathway<br>Signalling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyporproliferative Disorders").        | blood disorders (e.g., hypertension,<br>congositve heart failme, blood vessel<br>blockage, heart disease, stroke,<br>impource and ora described below<br>under "Immun Activity".  "Cardiovascular Disorders", and/or<br>"Blood-Related Disorders", immune<br>"Blood-Related Disorders", immune<br>disorders (e.g., as described below                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | disorder Timmuse, Activity.), neural disorders (eg. as described below disorders (eg. as described below how men's Yearled Activity and how how described Diseases'), and Neurological Diseases'), and suited on the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activity of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the activities of the | diabetes (e.g., ilabetic retinopally, diabetic retinopally, diabetic reproparably, kidney disease (e.g., renal ilabuet, reprinopally, kidney disease (e.g., renal ilabuet, reprinopally, denor of the disease and diseathers as described in the 'Renal Disouters' and escribed in the 'Renal Disouters' and the state of disease and nerve damage (e.g., reary disease and nerve damage (e.g., due to disherior transpathy, blood vessel blockage, incurred ordinetic neuropathy or blood vessel disherio neuropathy or blood vessel disherio neuropathy or blood vessel disherior neuropathy or blood vessel disherior neuropathy or blood vessel continsion, drowniess, mental continsion, drowniess, mental |
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| of each of which are herein incorporated by reference in its entirey. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., | through the ATC(2"9). Exemplary mouse adjooyte cells that may be used according to these assays include 373-Lt cells. 373-Lt is an adherent mouse preadineys cell line that is a continous subsenio of 313 finebals accleding through cells in the design of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of | pre-adjoorge or adjoose-like conversion under appropriate differentiation conditions known in the art.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's | contracture). An additional | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | indications are disorders of the | musculoskeletal systems including | myopathies, muscular dystrophy, | and/or as described herein. | Additional highly preferred | indications include, hypertension, | coronary artery disease, | dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, |
|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|-------------------------------------|----------------------------------------|---------------------------------|-----------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|-----------------------------------|---------------------------------|-----------------------------|-----------------------------|------------------------------------|--------------------------|---------------------------|-----------------------------------------|
|                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                    |                          |                           |                                         |
|                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                    |                          |                           |                                         |
| -                                   |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                    |                          |                           |                                         |

|                                                                                                                   | stroke, and other diseases and<br>disorders as described in the<br>"Cardiovascular Disorders" section |
|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Lochthead et al., Diahetes 49(6):896. P. 903 (2000); and Yeagley et al., 1 Biol Chen, 274(23):178(1-1782) (2000). | below), dyslipidemia, endocrine<br>disorders (as described in the<br>"Endocrine Disorders" section    |
| the contents of each of which is therein incorporated by reference in i                                           | oelow), neuropathy, vision<br>impairment (e.g., diabetic retinopathy                                  |
| its entirety. Hepatocyte cells that a may be used according to these                                              | and blindness), ulcers and impaired<br>wound healing, infection (e.g., an                             |
| assays are publicly available (e.g.,                                                                              | infectious diseases or disorders as                                                                   |
| _                                                                                                                 | Diseases" section below, especially                                                                   |
| ŭ                                                                                                                 | of the urinary tract and skin), carpal                                                                |
| according to these assays include the which contains a transition                                                 | tunnel syndrome and Dupuytren's                                                                       |
|                                                                                                                   | P                                                                                                     |
|                                                                                                                   | and/or complications associated with                                                                  |
| cAMP derivatives.                                                                                                 | obesity. Additional highly preferred                                                                  |
|                                                                                                                   | indications include weight loss or                                                                    |
|                                                                                                                   | alternatively, weight gain.                                                                           |
| 7                                                                                                                 | Additional nigniy preferred                                                                           |
|                                                                                                                   | indications are complications                                                                         |
|                                                                                                                   | associated with insulin resistance. Additional highly preferred                                       |
|                                                                                                                   | indications are disorders of the                                                                      |
|                                                                                                                   | musculoskeletal systems including                                                                     |
|                                                                                                                   | myopathies, muscular dystrophy,                                                                       |
|                                                                                                                   | and/or as described herein.                                                                           |
|                                                                                                                   | Additional highly preferred                                                                           |
|                                                                                                                   | indications include glycogen storage                                                                  |
|                                                                                                                   | disease (e.g., glycogenoses),                                                                         |
|                                                                                                                   | hepatitis, gallstones, cirrhosis of the                                                               |
|                                                                                                                   | iver, degenerative or necrotic liver                                                                  |
|                                                                                                                   | disease, alcoholic liver diseases,                                                                    |
|                                                                                                                   | librosis, liver regeneration, metabolic                                                               |
|                                                                                                                   | disease, dyslipidemia and cholesterol                                                                 |

|     |         |     |                  |                                       | metabolism, and henatocarcinomas.     |
|-----|---------|-----|------------------|---------------------------------------|---------------------------------------|
|     |         |     |                  |                                       | Highly preferred indications include  |
|     |         |     |                  |                                       | blood disorders (e.g., as described   |
|     |         |     |                  |                                       | below under "Immune Activity",        |
|     |         |     |                  |                                       | "Cardiovascular Disorders", and/or    |
|     |         |     |                  |                                       | "Blood-Related Disorders"), immune    |
|     |         |     |                  |                                       | disorders (e.g., as described below   |
|     |         |     |                  |                                       | under "Immune Activity"), infection   |
|     |         |     |                  |                                       | (e.g., an infectious disease and/or   |
|     |         |     |                  |                                       | disorder as described below under     |
|     |         |     |                  |                                       | "Infectious Disease"), endocrine      |
|     |         |     |                  |                                       | disorders (e.g., as described below   |
|     |         |     |                  |                                       | under "Endocrine Disorders"), and     |
|     |         |     |                  |                                       | neural disorders (e.g., as described  |
|     |         |     |                  |                                       | below under "Neural Activity and      |
|     |         |     |                  |                                       | Neurological Diseases").              |
|     |         |     |                  |                                       | Additional preferred indications      |
|     |         |     |                  |                                       | include neoplastic diseases (e.g., as |
|     |         |     |                  |                                       | described below under                 |
|     |         |     |                  |                                       | "Hyperproliferative Disorders").      |
|     |         |     |                  |                                       | Preferred indications include         |
|     |         |     |                  |                                       | neoplasms and cancers, such as,       |
|     |         |     |                  |                                       | leukemia, lymphoma, prostate,         |
|     |         |     |                  |                                       | breast, lung, colon, pancreatic,      |
|     |         |     |                  |                                       | esophageal, stomach, brain, and       |
|     |         |     |                  |                                       | urinary cancer. A highly preferred    |
|     |         |     |                  |                                       | indication is liver cancer. Other     |
|     |         |     |                  |                                       | preferred indications include benign  |
|     |         |     |                  |                                       | dysproliferative disorders and pre-   |
|     |         |     |                  |                                       | neoplastic conditions, such as, for   |
|     |         |     |                  |                                       | example, hyperplasia, metaplasia,     |
|     |         |     |                  |                                       | and/or dysplasia.                     |
| !   | HMADS41 | 541 | Protection from  | Caspase Apoptosis Rescue. Assays      | A highly preferred embodiment of      |
| 137 |         |     | Endothelial Cell | for caspase apoptosis rescue are well | the invention includes a method for   |
|     |         |     | Apoptosis.       | known in the art and may be used or   | sumulating endothelial cell growth.   |
|     |         |     |                  | routinely modified to assess the      | An alternative highly preferred       |
|     |         |     |                  | ability of the polypeptides of the    | embodiment of the invention           |

| invention) to influit espages preferre protesser-nediated apoptosis; remain proposition areas assays and apoptosis that may be used or routinely modified to test caspase profiler apoptosis that may be used or routinely modified to test caspase profiler and agonisis reares of the proplication of the invention (including anthodies inholded the assays disabled and agonisis or antiagonisis of the invention) include the assays and apoptosis or antiagonists of the invention (including anthodies). The profiler remains the test, 1882-194 (2000), Messme cluding the profiler test, 1882-194 (2000), Messme cluding information and populate of the agonism of the assays and the countries of each of histia are been in the countries of each of histia are been in the countries of each of histia are preferred incorporated by reference in its incorporated by reference in its contract of the assays include contract of the assays include according to these assays include decrease according to these assays include decrease horize and evidence of the profiler of the according to the according to the profiler of the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the according to the ac | and ansures a metion or intiming presented in the ansures a method for ansured and method for a minimaling emotionistic and and for a method for a minimation endothelial cell proliferation. An alternative highly prolifered emolecularies of the proliferation and alternative highly preferred emolecularies of the invention includes a method for infinition genedicibilial cell proliferation. A highly preferred methodriest of the invention includes a method for simulating method in the invention includes a method for inhibiting emotion of the invention includes a method for inhibiting preferred emolecial cell gas an embod for animating apoptosis of endothelial cell servation includes as method for animating apoptosis of cadothelial control of the invention for the control for inhibiting encodered animating apoptosis of endothelial cells. An alternative highly preferred emoleciment of the invention includes a method for simulating angeogenists. An alternative highly preferred emolecularies of the invention includes as method for simulating angeogenesis. An alternative highly preferred emolecularies of the invention includes as method for simulating among energies. A highly preferred emolecularies of the invention includes a method for simulating among energies as method for inhibiting among energies. A highly preferred emolecularies of the invention includes a method of infiniting among energies. An alternative highly preferred emolecularies of the invention includes a method of for inhibiting among energies. |
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| reduction alternation alternat | reducing cardae hyperrophy. An<br>alternative highly preferred<br>embodiment of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| cardiac hypertrophy. Highly preferred indications include namidatic diseases (a. g. dascribal |
|-----------------------------------------------------------------------------------------------|
| below under "Hyperproliferative<br>Disorders"), and disorders of the                          |
| cardiovascula system (e.g., heart<br>disease, congestive heart failure.                       |
| hypertension, aortic stenosis,                                                                |
| cardiomyopathy, valvular<br>regunstration. left ventricular                                   |
| dysfunction, atherosclerosis and                                                              |
| atherosclerotic vascular disease,                                                             |
| diabetic nephropathy, intracardiac shunt. cardiac hypertrophy.                                |
| myocardial infarction, chronic                                                                |
| hemodynamic overload, and/or as                                                               |
| described below under                                                                         |
| "Cardiovascular Disorders").                                                                  |
| Highly preferred indications include                                                          |
| cardiovascular, endothelial and/or                                                            |
| angiogenic disorders (e.g., systemic                                                          |
| diabetes mellitus, as well as diseases                                                        |
| of the vessels themselves, such as of                                                         |
| the arteries, capillaries, veins and/or                                                       |
| lymphatics). Highly preferred are                                                             |
| angiogenesis and/or                                                                           |
| cardiovascularization. Highly                                                                 |
| preferred are indications that inhibit                                                        |
| angiogenesis and/or                                                                           |
| cardiovascularization. Highly                                                                 |
| preferred indications include                                                                 |
| antiangiogenic activity to treat solid                                                        |
| tumors, leukemias, and Kaposi's                                                               |
| sarcoma, and retinal disorders.                                                               |
| Highly preferred indications include                                                          |

|  | neonlasms and cancer such as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|  | To be a consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the consequence of the conse |
|  | Naposi s sarcoma, nemangioma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | (capillary and cavernous), glomus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | tumors, telangiectasia, bacillary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | angiomatosis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | hemangioendothelioma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | angiosarcoma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | haemangiopericytoma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | lymphangioma, lymphangiosarcoma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | Highly preferred indications also                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | include cancers such as, prostate,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | breast, lung, colon, pancreatic,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | esophageal, stomach, brain, liver,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | and urinary cancer. Preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | indications include benign                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | dysproliferative disorders and pre-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | neoplastic conditions, such as, for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | example, hyperplasia, metaplasia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | and/or dysplasia. Highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|  | preferred indications also include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | arterial disease, such as,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | atherosclerosis, hypertension,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | coronary artery disease,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|  | inflammatory vasculitides,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | Reynaud"s disease and Reynaud"s                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | phenomenom, aneurysms, restenosis;                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | venous and lymphatic disorders such                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | as thrombophlebitis, lymphangitis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | and lymphedema; and other vascular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | disorders such as peripheral vascular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | disease, and cancer. Highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | preferred indications also include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | trauma such as wounds, burns, and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | injured tissue (e.g., vascular injury                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | such as, injury resulting from balloon                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | angioplasty, and atheroschlerotic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | lesions), implant fixation, scarring,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|         |     |               |                                  | ischemia reperfusion injury,          |
|---------|-----|---------------|----------------------------------|---------------------------------------|
|         |     |               |                                  | rheumatoid arthritis, cerebrovascular |
|         |     |               |                                  | renal failure and osteonorosis        |
|         |     |               |                                  | Additional highly preferred           |
|         |     |               |                                  | indications include stroke, graft     |
|         |     |               |                                  | rejection, diabetic or other          |
|         |     |               |                                  | retinopathies, thrombotic and         |
|         |     |               |                                  | coagulative disorders, vascularitis,  |
|         |     |               |                                  | lymph angiogenesis, sexual            |
|         |     |               |                                  | disorders, age-related macular        |
|         |     |               |                                  | degeneration, and treatment           |
|         |     |               |                                  | /prevention of endometriosis and      |
|         |     |               |                                  | related conditions. Additional highly |
|         |     |               |                                  | preferred indications include         |
|         |     |               |                                  | fibromas, heart disease, cardiac      |
|         |     |               |                                  | arrest, heart valve disease, and      |
|         |     |               |                                  | vascular disease. Preferred           |
| _       |     |               |                                  | indications include blood disorders   |
| _       |     |               |                                  | (e.g., as described below under       |
|         |     |               |                                  | "Immune Activity", "Blood-Related     |
|         |     |               |                                  | Disorders", and/or "Cardiovascular    |
| _       |     |               |                                  | Disorders"). Preferred indications    |
| _       |     |               |                                  | include autoimmune diseases (e.g.,    |
|         |     |               |                                  | rheumatoid arthritis, systemic lupus  |
|         |     |               |                                  | erythematosis, multiple sclerosis     |
|         |     |               |                                  | and/or as described below) and        |
|         |     |               |                                  | immunodeficiencies (e.g., as          |
|         |     |               |                                  | described below). Additional          |
|         |     |               |                                  | preferred indications include         |
|         |     |               |                                  | inflammation and inflammatory         |
|         |     |               |                                  | disorders (such as acute and chronic  |
|         |     |               |                                  | inflammatory diseases, e.g.,          |
|         |     |               |                                  | inflammatory bowel disease and        |
|         |     |               |                                  | Crohn's disease), and pain            |
|         |     |               |                                  | management.                           |
| HMADS41 | 541 | Activation of | Kinase assay. Kinase assays, for | A highly preferred embodiment of      |
|         |     |               |                                  |                                       |

| Hepatocyte ERK Sganling Pathway File K signal manadorion hat regulate cell politeration or differentiation used or routinely modified to assess the ability of polyperpidies of the invention (including anthodics and againsts or attactivition, and differentiation. Exemplery assays for invention (including anthodics and differentiation. Exemplery assays for HRK k innes estivity that may be used or routinely modified to use IRK k innes estivity that may be used or routinely modified to use IRK k innes estivity that may be used or routinely modified to use IRK k innes estivity that may be used or routinely modified to use IRK k innes estivity that may be used or routinely modified to use IRK k innes estivity that may be used or properties of the invention) include the assays disclosed in Forner or al.  (1998); Kyrinkis JA, Biochem Soc Syap, HO, HO, 1999; Chang and Kaini, Nature 410(6524);7-40 (1998); Kyrinkis JA, Biochem Soc Orio, and Cobal MI, Pop Biophys Mol Biol JT(CA-Jy-79-50) (1999).  The contents of cond or finds an may be used scording to or these assays include Halle cells, which are known to reAMP derivatives. | stimulating thereunds in cludes a method for stimulating the protective of the cludes and the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes of the cludes                                                                                                                                                                                                                                                                                                    | highly preferred enhodiment of the injury preferred enhodiment of the invention includes a method for activating beparedy cells. An alternative highly preferred enhodiment of the invention includes an enchol for inhibiting the activation of and/or inactivating hepatocyte cells. Highly preferred indexions include disorders of the indexions include disorders of the indications include disorders of the state and or activation disorders of the state of the individual disorders of the state of the individual disorders of the state of the individual disorders of the state of the individual disorders of the state of the individual disorders of the state of the individual disorders of the state of the individual disorders of the state of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual disorders of the individual dis | recorders", Preferred indications include reoplastic diseases (e.g., as described below under "Happerpoliterative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "C'entiovuscular Disorders", immune disorders (e.g., as described below under "Immune Activity", neural disorders (e.g., as described below under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Immune Activity", neural under "Neural Activity und |
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| Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | verygle in Iller, Itanse seasy, for<br>IRR signal transduction that regular<br>cell proliferation or differentiation<br>cell proliferation or differentiation<br>are well known in the art and may be<br>used or routinely modified to assess<br>the ability of properties of the<br>investion (forduling antibodies and<br>investion) forduling antibodies and<br>investion) to promote or inhibit cell<br>investion) to promote or inhibit cell<br>investion) to promote or inhibit cell<br>investion) to promote or inhibit cell<br>investion. Is exemplery assays for<br>differentiation. Exemplery assays for<br>the first of the control of the con-<br>trol of the control of the con-<br>trol of the control of the con-<br>trol of the control of the con-<br>trol of the control of the con-<br>trol of the control of the con-<br>trol | polypeptides of the inventions of the measurement of the debt of t | herein incorporated by reference in its entirety. Rat liver beyanom cells that may be used according to these associated variable (e.g., through the ATCCPA). Exemplary including the ATCCPA incorporate in the representation of the area of the area of the area include. Helle cells, which are known to respond to glucocorticoids, insulin, or exharitves.                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Hepatocyte ERK<br>Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| _ |  | Neurological Diseases"), and                                              |
|---|--|---------------------------------------------------------------------------|
|   |  | under "Infectious Disease").                                              |
|   |  | ind                                                                       |
|   |  | diabetes mellitus. An additional highly preferred indication is a         |
|   |  | complication associated with                                              |
|   |  | diabetes (e.g., diabetic retinopathy,                                     |
|   |  | diabetic nephropathy, kidney disease<br>(e.g., renal failure, nephropathy |
|   |  | and/or other diseases and disorders as                                    |
|   |  | described in the "Renal Disorders"                                        |
|   |  | section below), diabetic neuropathy,                                      |
|   |  | nerve disease and nerve damage                                            |
|   |  | (e.g., due to diabetic neuropathy),                                       |
|   |  | blood vessel blockage, heart disease,                                     |
|   |  | stroke, impotence (e.g., due to                                           |
|   |  | diabetic neuropathy or blood vessel                                       |
|   |  | blockage), seizures, mental                                               |
|   |  | confusion, drowsiness, nonketotic                                         |
|   |  | hyperglycemic-hyperosmolar coma,                                          |
|   |  | cardiovascular disease (e.g., heart                                       |
|   |  | disease, atherosclerosis,                                                 |
|   |  | microvascular disease, hypertension,                                      |
|   |  | stroke, and other diseases and                                            |
|   |  | disorders as described in the                                             |
|   |  | "Cardiovascular Disorders" section                                        |
|   |  | below), dyslipidemia, endocrine                                           |
|   |  | disorders (as described in the                                            |
|   |  | "Endocrine Disorders" section                                             |
|   |  | below), neuropathy, vision                                                |
|   |  | impairment (e.g., diabetic retinopathy                                    |
|   |  | and blindness), ulcers and impaired                                       |
|   |  | wound healing, infection (e.g.,                                           |
|   |  | infectious diseases and disorders as                                      |
|   |  | described in the "Infectious                                              |
|   |  | Diseases" section below, especially                                       |

| of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's | contracture). An additional highly | preferred indication is obesity and/or | complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | indications are disorders of the | musculoskeletal systems including | myopathics, muscular dystrophy, | and/or as described herein. | Additional highly preferred | indications include, hepatitis, | jaundice, gallstones, cirrhosis of the | liver, degenerative or necrotic liver | disease, alcoholic liver diseases, | fibrosis, liver regeneration, metabolic | disease, dyslipidemia and | chlolesterol metabolism. | Additional highly preferred | indications include neoplasms and | cancers, such as, hepatocarcinomas, | other liver cancers, and colon and | pancreatic cancer. Preferred | indications also include prostate, | breast, lung, esophageal, stomach, | brain, and urinary cancer. Other | preferred indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, |
|----------------------------------------|---------------------------------|------------------------------------|----------------------------------------|-------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|-----------------------------------|---------------------------------|-----------------------------|-----------------------------|---------------------------------|----------------------------------------|---------------------------------------|------------------------------------|-----------------------------------------|---------------------------|--------------------------|-----------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------|------------------------------------|------------------------------------|----------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|
|                                        |                                 |                                    |                                        |                               |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                 |                                        |                                       |                                    |                                         |                           |                          |                             |                                   |                                     |                                    |                              |                                    |                                    |                                  |                                      |                                     |                                     |                                   |
|                                        |                                 |                                    |                                        |                               |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                 |                                        |                                       |                                    |                                         |                           |                          |                             |                                   |                                     |                                    |                              |                                    |                                    |                                  |                                      |                                     |                                     |                                   |
|                                        |                                 |                                    |                                        |                               |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                 |                                        |                                       |                                    |                                         |                           |                          |                             |                                   |                                     |                                    |                              |                                    |                                    |                                  |                                      |                                     |                                     |                                   |

| invention include using polyapstides of the invention include using polyapstides of the invention (or antibodies, agonists, or antagonists thereof) in any or antagonists, prevention, and or treatment of sadma, allergy, hypersensitivity and inflammation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Stepase Apoptosis are well known in engages apoptosis are well known in modified to assess the ability of properties of near and may be used or routinely modified to assess the ability of hopeptides of the invention in organic assess the ability of properties of the invention in crapital craspores in immune cells (such as for example; in mast cells). Must for example; in mast cells). Must for example; in mast cells). Must muscal insues in connective and muscas insues in connective and muscas in state of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the invention of allergic disease. Daverglation of caspase apoptosis a further than the properties of the invention include the assays diseased in Mustan A. C. 261 13 (2001). Yestuman CF 2nd, et al. FEBN Lett 485(2)—21 103 (2001). Yestuman (T. 2nd, 13 Visse Res 37(3). 75-80 (1996), the Properties of the control of the chiefs in the better in the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of |
| Regulation of apoptosis of immune cells (such as mast cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 175                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HNAADS41                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 133                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                                                                                                                                                                                                                                                                                                                                                | diabetes mellins.  A highly preferred indication is dealeress mellins.  In diabetes mellins.  A complication associated with diabetes region of diabetes of diabetic retinopathy, diabete diabetes (e.g., diabetic retinopathy, diabete, repropathy, lekture/disease (e.g., rotal faither, rephropathy lekture/diseases and diseates and diseates and diseates and diseates and diseates and diseates and there diamege (e.g., the off induction remopathy, nerve diseases and there diamege (e.g., the off induction remopathy or blood vessel blockegs, heart diseases, section flowed, and prepared menderic neuropathy or blood vessel blockegs, heart diseases, mend contission, dowsiness, montal contission, dowsiness, montal contission, diameter contained and seases (f.g., then the diseases) and diseased ease described in the diseases and diseased ease described in the "Hiddeorine Diseaders" section below), displaced se described in the "Hiddeorine Diseaders" section below), displaced se described in the "Hiddeorine Diseaders" section below), displaced se described in the "Hiddeorine Diseaders" section helps, is soon in maniturent (e.g., diabetic retinopathy). |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| entirety, Immune cells that may be produced according to these sassys are publicly available (e.g., through connected sources). Exemplary immune cells that may be used according to these assays include according to these assays include mass cells such as the HMC human must cell such as the HMC human must cell such as the HMC human must cell such as | are swear for each man are well-known in the are well-known in the are and may be the shifts of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptics of the invention of polygoptic and polygoptic of the polygoptic calcium cannot be polygoptic calcium content of the polygoptic calcium content of the polygoptic calcium content of the polygoptic calcium polygoptics of the invention of calcium, leading to activation of calcium, pedain responsive signaling puthways and alterations in cell manuels. Each of polypoptics of the invention included may be used or routinely undrifted to polypoptics of the invention included and polypoptics of the invention included and polypoptics of the invention included and polypoptics and agonts to antagonists of the invention included and polypoptics and agonts to Enderindogy, 136(10):438-641.                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                | Simulation of Calcium<br>Calk, in pancreatic beta<br>cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                | 542                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                | HMAMILS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                | 138                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|     |         |     |                             | Cadaim 1989 New-Dec;10(8):555-61<br>(1989), the contents of each of which<br>its entirety. Panceteaic of the third<br>street in convented by reference in<br>its entirety. Panceteaic cells that may<br>be treet a convented by reference in<br>its entirety. Panceteaic cells that may<br>retrofy and on the convented<br>publishy available (e.g., through the<br>ACCO <sup>3</sup> ) and/on two be routinely<br>generated. Exemplary pancetaic<br>cells that may be undirely<br>generated. Exemplary pancetaic<br>of the cells that may be undirely<br>extensively and the cells that the<br>cells in each state of the cells and<br>only a cells of the cells of the<br>sommostatin, and gluevoorifooid<br>commostatin, and gluevoorifooid<br>which is simulated by gluevoer tooid<br>sommostatin or gluevoorifooid.<br>Askenoti. Buckenn. J. 19: 547-551. | wound healthing, and infection (e.g., infections diseases and disorders as foresteened infection (e.g., infections diseases and disorders as Diseases's section below, capacity the forest of the unimary treat and skin), campal turnel syndrome and Dugwytern's contracture). An additional highly preferred indication is obesity and and additional subject of the configuration is associated with obesity. Additional highly preferred alternatively, weight gain.  Additional highly preferred alternatively, weight gain.  Additional highly preferred indications inductive single-state and and indications are complications associated with instalin resistance. |
|-----|---------|-----|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 138 | HMAMIIS | 542 | Activation of Transcription | are swell-known in the art and may be well-known in the art and may be well-known in the art and may be add and routinely medified to assess ability of polypeptides of the invention to inhibit or activate invention to inhibit or activate masserphon. An example of such an assay follows: Cells were pretreated as 1831 supermannes to controls for 15-18 hours. SIAP activity was an epithesial colon adenocarionna or optithesial colon adenocarionar an epithesial colon adenocarionar mice make cell line. ISI varI a model mice make cell line LSIAT a model mice make cell line LSIAT a model                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| wound healing and includion (e.g., includion sliessess and disorders as Disearches in Thickings Disearches section below, especially additional highly preferred indication associated visib obesity. Additional additional highly preferred includion associated visib obesity. Additional bighly preferred includions associated visib obesity, vociglat (period, Additional highly preferred includions are complications associated visib includiors associated visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visible visibl | A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabete retinopalty, kidney disease diabetic nephropathy, kidney disease. |
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| 27(23):14282-25 (1998), Mora, S. et al., J Biol Chem, 27(42):1632-3 (2000), Lin M., Le al., J Biol Chem, 27(45):1632-3 (2000), Lin M., Le al., J Biol Chem, 27(45):28514-21 (1994), regulatory element and nord DNA regulatory element and nord DNA human GLUT4 promoter in a management meet. J Biol Chem, 2000 Aug. 427(51):2366-73; Breger, et al., Grave 66:141 (1988); and. Aug. 427(51):2366-73; Breger, et al., Grave 66:141 (1988); and. Gullern, J. et al. Methods, and. Grave 66:141 (1988); and. Erroynal, 12(3-52-368 (1992), the control of each of vibrids is herein incomparated by reference in securities of each of vibrids is herein monents of each of vibrids is and conditing by generated. Exemplary cells that may be used excoding to these assays include the mones 573-1.1 cells are a continuous substantin of 373 flibroblass developed through clothal line. Mones 573-1.1 cells are a disposyte to adipose-like conversation outlines appropriate differentiation culture conditions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Regulation of<br>transcription through<br>the PEPCK promoter in<br>hepatocytes                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 544                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HMDAB56                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 140                                                                                                                                                                                                                       |

| athy                                  | isorders as                                                                  | propathy,                             | mage                              | oathy),                             | rt disease,                           | ot c                                 | d vessel                             |                                     | ketotic                             | lar coma,                        | , heart                                |                                     | ertension,                           | pu                             | 9                                   | section                            | crine                                | he                                     | ion                              |                                  | etinopathy                             | mpaired                             | .g., an                            | ders as                              |                                   | specially                            | n), carpal                             | ytren's                           | onal                                  | is obesity                             | iated with                           | ргебетед                             | loss or                            |                             |                             |
|---------------------------------------|------------------------------------------------------------------------------|---------------------------------------|-----------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|----------------------------------|----------------------------------|----------------------------------------|-------------------------------------|------------------------------------|--------------------------------------|-----------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|
| (e.g., renal failure, nephropathy     | and/or other diseases and disorders as<br>described in the "Renal Disorders" | section below), diabetic neuropathy,  | nerve disease and nerve damage    | (e.g., due to diabetic neuropathy). | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to      | diabetic neuropathy or blood vessel  | blockage), seizures, mental         | confusion, drowsiness, nonketotic   | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart    | disease, atherosclerosis,           | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine      | disorders (as described in the         | "Endocrine Disorders" section    | sclow), neuropathy, vision       | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., an | infectious diseases or disorders as  | described in the "Infectious      | Diseases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's   | ture). An additional                  | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred |
| (e.g., n                              | and/or                                                                       | section                               | nerve c                           | (e.g., d                            | blood                                 | stroke,                              | diabeti                              | blocka                              | confus                              | hyperg                           | cardio                                 | disease                             | microv                               | stroke,                        | disorde                             | "Cardi                             | below)                               | disorde                                | "Endoc                           | below)                           | impain                                 | and bli                             | monup                              | infection                            | describ                           | Discasi                              | of the 1                               | tunnel                            | contracture).                         | highly                                 | and/or                               | obesity                              | indicat                            | alterna                     | Addition                    |
| (including antibodies and agonists or | antagomsts of the invention) to<br>activate the PEPCK promoter in a          | reporter construct and regulate liver | gluconeogenesis. Exemplary assays | for regulation of transcription     | through the PEPCK promoter that       | may be used or routinely modified to | test for PEPCK promoter activity (in | hepatocytes) of polypeptides of the | invention (including antibodies and | agonists or antagonists of the   | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in          | Enzymol 216:362-368 (1992);    | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988);           | Lochhead et al., Diabetes 49(6):896- | 903 (2000); and Yeagley et al., J Biol | Chem 275(23):17814-17820 (2000), | the contents of each of which is | herein incorporated by reference in    | its entirety. Hepatocyte cells that | may be used according to these     | assays are publicly available (e.g., | through the ATCCTM) and/or may be | routinely generated. Exemplary liver | hepatoma cells that may be used        | according to these assays include | H4lle cells, which contain a tyrosine | amino transferase that is inducible    | with glucocorticoids, insulin, or    | cAMP derivatives.                    |                                    |                             |                             |
|                                       |                                                                              |                                       |                                   |                                     |                                       |                                      |                                      |                                     |                                     |                                  |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |
|                                       |                                                                              |                                       |                                   |                                     |                                       |                                      |                                      |                                     |                                     |                                  |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |
|                                       |                                                                              |                                       |                                   |                                     |                                       |                                      |                                      |                                     |                                     |                                  |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |
|                                       |                                                                              |                                       |                                   |                                     |                                       |                                      |                                      |                                     |                                     |                                  |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |

|  | indications are complications           |
|--|-----------------------------------------|
|  | organization on groundstate             |
|  | associated with insulin resistance.     |
|  | Additional highly preferred             |
|  | indications are disorders of the        |
|  | musculoskeletal systems including       |
|  | myopathies, muscular dystrophy,         |
|  | and/or as described herein.             |
|  | Additional highly preferred             |
|  | indications include glycogen storage    |
|  | disease (e.g., glycogenoses),           |
|  | hepatitis, gallstones, cirrhosis of the |
|  | liver, degenerative or necrotic liver   |
|  | disease, alcoholic liver diseases,      |
|  | fibrosis, liver regeneration, metabolic |
|  | disease, dyslipidemia and cholesterol   |
|  | metabolism, and hepatocarcinomas.       |
|  | Highly preferred indications include    |
|  | blood disorders (e.g., as described     |
|  | below under "Immune Activity",          |
|  | "Cardiovascular Disorders", and/or      |
|  | "Blood-Related Disorders"), immune      |
|  | disorders (e.g., as described below     |
|  | under "Immune Activity"), infection     |
|  | (e.g., an infectious disease and/or     |
|  | disorder as described below under       |
|  | "Infectious Disease"), endocrine        |
|  | disorders (e.g., as described below     |
|  | under "Endocrine Disorders"), and       |
|  | neural disorders (e.g., as described    |
|  | below under "Neural Activity and        |
|  | Neurological Diseases").                |
|  | Additional preferred indications        |
|  | include neoplastic diseases (e.g., as   |
|  | described below under                   |
|  | "Hyperproliferative Disorders").        |
|  | Preferred indications include           |
|  | neoplasms and cancers, such as,         |

| 141 HMEBD18 |     |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | esoplaged, somach, panteauc, esoplaged, somach, brain, and trainer cancer. Alighly preferred indication is liver cancer. Other preferred indications include benign objectives in the cancer condemy to the conditions, such as the conditions, such as, for nonplastic conditions, such as, for any example, hypothesis, metaplisis, and any example, physical series and pre-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------|-----|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             | 245 | Strandation of Codium | aways for measuring calcium flux are weel-known in the art and may be used or routinely modified to assess the ability of polyperidies of the invention (including antibodies and invention) (including antibodies and invention) to including antibodies and invention) to mobilitiz calcium. For example, the PLER sassy may be used to measure influx of calcium. For a concentrations of cytosostic calcium concentrations of cytosostic calcium concentrations of cytosostic calcium concentrations of cytosostic calcium concentrations of cytosostic calcium concentrations of cytosostic calcium concentrations of calcium. Extracellular estimate salcium. Extracellular calcium. Extracellular calcium. Extracellular calcium, estimation of calcium, leading to activation of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that mays be used or notunely modified to measure calcium into two seasons disclated in Saint I.S. et al., (1958)-Molegani II. et al., et al., (1958)-Molegani II. et al., et al., (1958)-Molegani II. et al., | A highly preferred indication is dishese methins a delitional highly preferred indication is additional highly preferred indication disheres return as complication associated with disheres (e.g., dishefut returnpositiv, dishered indication disheres (e.g., dishefut returnpositiv, dishered instances and dishered to additionally kidney disease (e.g., renal failure, hephropathy and color diseases and disheric neuropathy, nerve disease and nerve damage (e.g., due to disheric neuropathy). Honor vessel blockage, heart disease, can block age, heart disease, can block age, and the disheric neuropathy or blood vessel blockage, heart disease, can disheric neuropathy or blood vessel blockage, heart means of disheric neuropathy or blood vessel blockage, heart means of disheric neuropathy or blood vessel blockage, heart disease, meand confliction (lovositors) means of the disheric sease, hyperension, hyperglycennic-hyperosanolar coma, essences, and other diseases and dishorders as described in the Cardiovascular Disorders's section disorders (ed seeribed in the |

|         |     |                                                                                                                   | Hopes, Richarden SB, et al., Biodema J, S88 (P. 8).847-81. Biodema J, S88 (P. 8).847-81. Biodema J, S88 (P. 8).847-81. Biodema J989 (No-bee, 10/8).558-41. Call Calcium J989 (No-bee, 10/8).558-41. Galactic Hopes, Breen in sopropared by reference in servation colls that may be realized by reference in sentiency. Puncreatic cells that may be break a souther of e.g., through the ArtiCryan andre may be routinely generated. Exemplary paraceatic estimation practication of the seasons include HITT15 Cells. Breamplary paraceatic estimation of the seasons include HITT15 Cells. Breamplary paraceatic estimation of the catalogue and supervised by Strian humaner issie cells ransformed with humaner issie cells ransformed with sammlaced by glacose and which is simulated by glacose and which is simulated by glacose and which is simulated by glacose and Ashkroft. Richelm J. 219, 547-551. | impainment (e.g., diabetic retinopathy and blandses), ulees and impained and blandses), ulees and intention (e.g., intections of issuess and discours and intections of issuess and discours and blandses). Intections of its urman year and skin, campal tunnel syndrome and Dupptynen's consecuence. An additional highly preferred indication is obesity and an additional highly preferred indication is associated with obesity. Additional highly preferred indication is obesity in discourse including the preferred alternatively, weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. |
|---------|-----|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HMEED18 | 545 | Production of RANTES<br>in endotheial cells<br>(casch as human<br>umbilical vein<br>endothelial cells<br>(HUVEC)) | Sancret Hocken, 1219; 347-531; Sancret et al. Proc. Natl. Acad. Sci. Son. Res. 843-843; 1981. RANTES FMAT. Assays for Immunocondulatory proteins that induce chemotris of T cells frown in the rar and may be used or rouninely modified to assays the inventory including authorities of the inventory in the part and may be used or rouninely modified to assays the inventory including authorities of the inventory including authorities of the inventory including authorities of the inventory including authorities of the inventory including authorities of the invention of nondaine                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|                                    |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      |                                 |                                   |                                    |                                     |                                       |                                       |                                | A highly preferred indication is |
|------------------------------------|----------------------------|--------------------------------|------------------------------------|--------------------------------------|------------------------------|---------------------------------|-------------------------------------|-------------------------------|------------------------------|-------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-----------------------------|-------------------------------------|-------------------------------------|----------------------------------|---------------------------------------|------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------------|-------------------------------------|--------------------------------------|---------------------------------|-----------------------------------|------------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------|----------------------------------|
| chemotaxis, and/or mediate humoral | or cell-mediated immunity. | Exemplary assays that test for | immunomodulatory proteins evaluate | the production of cytokines, such as | RANTES, and the induction of | chemotactic responses in immune | cells. Such assays that may be used | or routinely modified to test | immunomodulatory activity of | polypeptides of the invention | (including antibodics and agonists or | antagonists of the invention) include | the assays disclosed in Miraglia et | al., J Biomolecular Screening 4:193- | 204 (1999); Rowland et al., | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000): Cocchi et | al., Science 270(5243);1811-1815 | (1995); and Robinson et al., Clin Exp | Immunol 101(3):398-407 (1995), the | contents of each of which are herein | incorporated by reference in its | entirety. Endothelial cells that may | be used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary endothelial | cells that may be used according to | these assays include human umbilical | vein endothelial cells (HUVEC), | which are endothelial cells which | line venous blood vessels, and are | involved in functions that include, | but are not limited to, angiogenesis, | vascular permeability, vascular tone, | and immune cell extravasation. | Caspase Apoptosis. Assays for    |
|                                    |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       | _                                     |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      |                                 |                                   |                                    |                                     |                                       |                                       |                                | Regulation of apoptosis          |
|                                    |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      |                                 |                                   |                                    |                                     |                                       |                                       |                                | 546                              |
| _                                  |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      |                                 |                                   |                                    |                                     |                                       |                                       |                                | HMEFT54                          |
|                                    |                            |                                |                                    |                                      |                              |                                 |                                     |                               |                              |                               |                                       |                                       |                                     |                                      |                             |                                     |                                     |                                  |                                       |                                    |                                      |                                  |                                      |                                       |                                       |                                             |                                     |                                      |                                 |                                   |                                    |                                     |                                       |                                       |                                |                                  |

| _                                                                                                                                                                                          |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic rephropathy, kidney disease                  | (e.g., reral failure, nephropathy<br>and/or other diseases and disorders as<br>described in the "Renal Disorders"<br>section below), disbetic neuropathy,<br>nerve disease and nerve damage<br>(e.g., due to diabetic neuropathy),    | blodd vessel blodegg, heard desaw,<br>stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel<br>blodegags), seztraces, mental<br>conthision, drowsiness, nonkeotic<br>hyperglycemic-hyperosmolar coma,<br>aculovascular disease (e.g., heart<br>disease, atherosis, | microwascular disease, inpertension, sees, and consider diseases, information of diseases and disorders as described in the Cardiovascular biostders' section bedow), dyslindermis, endocrine bedow), dyslindermis, endocrine disorders' section bedow), neuropathy, vision impairment (e.g., diabetic reinopathy and blindress), tuleers and impaired and blindress), tuleers and impaired and infections diseases and disorders is excepted in the described in the "infectious diseases" section below, especially blindress, but the dispersion of the diseases, section below, especially blindress, section below, especially | of the urinary tract and skin), carpal<br>unnel syndrome and Dupuytren's<br>contracture). An additional<br>highly preferred indication is obesity        |
| caspase apoptosis are well known in<br>the art and may be used or routinely<br>modified to assess the ability of<br>polypeptides of the invention<br>(including antibodies and agonists or | antagonists of the invention) to<br>promote caspase protesta-encediated<br>apoptosis. Apoptosis in pancreatic<br>beta is associated with induction and<br>progression of diabetes. Exemplary<br>assays for caspase apoptosis that may | be used rouningly modified to test<br>capase apoptosis activity of<br>polypeptides of the invention<br>(including anthodies and agomiss or<br>antagonists of the invention) include<br>the assays disclosed in: Loweth, AC,<br>et al., FBBS Lett, 400(6);285-8                      | Moff Biol Int. 39(6):1229-26 (1996).  124(4):687-27 (1996).  124(4):687-34 (2000); Chamfan, 1, 2, 4, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | are herein incorporated by reference<br>in its entirety. Pancreatic cells that<br>may be used according to these<br>assays are publicly available (e.g., |
| in pancreatic beta cells.                                                                                                                                                                  |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                          |
|                                                                                                                                                                                            |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                          |
| 142                                                                                                                                                                                        |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                          |

| and/or complications associated with obesity. Additional highly preferred indications nicited weight less or indications nicited weight gain. Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | highly preferred inclucions include inflammation (scute and chronic).  The senses, a three-centers, assima and allergy. Highly preferred indications include the include the include the inflammation and inflammation disorders, inmunological disorders, neoplastic disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders (such as and earthorsealth disorders). Highly preferred Disorders' Highly preferred Disorders' Highly preferred cancers such as, for example, entering indications include nephasing and call carcinoma, and prostate, large look paracterie, esophageal, somach, brain, liver and indications include bearing.                                                  |
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| the through the ATCCPV and/or may be routinely generated. Exemplary parterestic cells that may be used according to these assessys include RNAm. RNAm is a rat addresent RNAm. RNAm is a rat addresent line derived from a radiation induced line derived from a radiation induced by the cells produce and secrete islet. The cells produce and secrete islet instancial, and produce and secrete islet instancial, and the cells produce and secrete islet. The cells produce and secrete islet. The cells produce and secrete islet. The cells produce and secrete islet. The cells produce and secrete islet. The cells produce and secrete islet. Act and secrete islet in the produce and secrete islet. The cells produce and secrete islet. The cells produce and secrete islet. | induchatical cells, which are cells that line blood vessels, and are involved in metaons that include, but are not limited to, sangiogenesis, voscular promocell terrorseation. Exemplary voscular rows, and mamor cell terrorseation. Exemplary outdottelial cells that many be useful in CAM Cells that may be useful in the expression of ICAM (CIS4), and are available from commercial sources, and ICAM ceptression is important in mediating immane and inflammatory to open conducting tell in measing seading to spression of ICAM and and may be used or expression in the and may be used or contributed to the incredious leading copression of ICAM and may be used or demand of ICAM and may be used or promitively modified to assess the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Aboution of ICAM in<br>endotheila Calls (such<br>amma umbilical<br>vein endotheila cells<br>(HUVEC)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | £                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HMEGF92                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 143                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| dyspublicative disorders and pre-<br>propriatic conditions, such as, for<br>example, hypophasia, metaphasia,<br>and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | A highly preferred indication is disheres mellitus. A highly preferred indication is a complication associated with disheres regional properties and an advantage of the second properties and a second properties of the second properties and advantage of the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and the second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second properties and second proper |
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| ability of polypspides of the mericatio (trobing antibodies and agonists or antagonists of the contraction (trobinging antibodies and agonists or antagonists of the commercian (trobinging antibodies and the captes and the captes as the captes and the captes as the captes and the captes as the captes and the captes as the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and the captes and th | espase Apopusis a seasy for cospase gropusis are well known in modified to assess the ability of polyperkides of the invention) to polyperkides of the invention) to polyperkides of the invention) to promote caspase protease-mediated apoptosis, Apoptosis in panceratic apoptosis, Apoptosis in panceratic apoptosis, Apoptosis in panceratic apoptosis, Apoptosis in panceratic apoptosis, Apoptosis in panceratic apoptosis, apoptosis in panceratic apoptosis, apoptosis in panceratic apoptosis in panceratic apoptosis, apoptosis in panceratic apoptosis in panceratic apoptosis in panceratic apoptosis and apoptosis and in an apoptosis and apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an apoptosis and an ap |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 547                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|   | the ability of polypeptides of the           | diabetes (e.g., diabetic retinopathy,  |
|---|----------------------------------------------|----------------------------------------|
|   | invention (including antibodies and          | diabetic nephropathy, kidney disease   |
|   | agonists or antagonists of the               | (e.g., renal failure, nephropathy      |
|   | invention) to regulate viability and         | and/or other diseases and disorders as |
|   | proliferation of pancreatic beta cells.      | described in the "Renal Disorders"     |
|   | For example, the Cell Titer-Glo              | section below), diabetic neuropathy,   |
|   | luminescent cell viability assay             | nerve disease and nerve damage         |
|   | measures the number of viable cells          | (e.g., due to diabetic neuropathy),    |
|   | in culture based on quantitation of          | blood vessel blockage, heart disease,  |
|   | the ATP present which signals the            | stroke, impotence (e.g., due to        |
|   | presence of metabolically active             | diabetic neuropathy or blood vessel    |
|   | cells. Exemplary assays that may be          | blockage), seizures, mental            |
|   | used or routinely modified to test           | confusion, drowsiness, nonketotic      |
|   | regulation of viability and                  | hyperglycemic-hyperosmolar coma,       |
|   | proliferation of pancreatic beta cells       | cardiovascular disease (e.g., heart    |
|   | by polypeptides of the invention             | disease, atherosclerosis,              |
|   | (including antibodics and agonists or        | microvascular disease, hypertension,   |
|   | antagonists of the invention) include        | stroke, and other diseases and         |
|   | assays disclosed in: Friedrichsen BN,        | disorders as described in the          |
|   | et al., Mol Endocrinol, 15(1):136-48         | "Cardiovascular Disorders" section     |
|   | (2001); Huotari MA, et al.,                  | below), dyslipidemia, endocrine        |
|   | Endocrinology, 139(4):1494-9                 | disorders (as described in the         |
|   | (1998); Hugl SR, et al., J Biol Chem         | "Endocrine Disorders" section          |
|   | 1998 Jul 10;273(28):17771-9 (1998),          | below), neuropathy, vision             |
|   | the contents of each of which is             | impairment (e.g., diabetic retinopathy |
|   | herein incorporated by reference in          | and blindness), ulcers and impaired    |
|   | its entirety. Pancreatic cells that may      | wound healing, and infection (e.g.,    |
|   | be used according to these assays are        | infectious diseases and disorders as   |
|   | publicly available (e.g., through the        | described in the "Infectious           |
|   | ATCC <sup>TM</sup> ) and/or may be routinely | Diseases" section below, especially    |
| _ | generated. Exemplary pancreatic              | of the urinary tract and skin), carpal |
|   | cells that may be used according to          | tunnel syndrome and Dupuytren's        |
|   | these assays include rat INS-1 cells.        | contracture). An additional highly     |
|   | INS-1 cells are a semi-adherent cell         | preferred indication is obesity and/or |
|   | line established from cells isolated         | complications associated with          |
|   | from an X-ray induced rat                    | obesity. Additional highly preferred   |
|   | transplantable insulinoma. These             | indications include weight loss or     |

|     |         |     |                                                                                                                         | available (e.g., through the ATIC/TV) available (e.g., through the ATIC/TV) Exemplary pancreatic cells that may be not according to these usays include at INS-L cells. INS-L cells are a semi-adherent cell line are a semi-adherent cell line are a semi-adherent cell line are a semi-adherent cell line are a semi-adherent cell line are a semi-adherent cell line are a semi-adherent cell line are semi-adherent cell line are semi-adherent cell line are semi-adherent cell line are semi-adherent cell line are semi-adherent cell intention are semi-adherent cells insulant characteristics typical of mative paractaic bear cells including glucose inducible insulin secretion.                                                                                                                       | Diseases' section below, especially between the first times to biseases' section below, especially turned syndrome and Dispuyeren's for turner times and Dispuyeren's An additional highly preferred indication is obesity and or complications associated with one or complications associated with one or complications associated with and or complications include weight loss or indications include weight loss or indications include weight loss or Additional lightly preferred indications are complications associated with instillur resistance.                                                                                                             |
|-----|---------|-----|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 949 | HMSJU68 | 989 | transcription through<br>transcription through<br>NFRB response<br>delenent in immune<br>cells (such as EOL)<br>cells). | transarription through the VRBs response element are well-known in the reason element are well-known in the reason element are well-known in the ran and may be used or routinely modified to assess the ability of polyperdises of the invention (including antibodies and agonisis or amagenists of the invention) to regulate VRBs transcription florose and appearance of the company genes. Exemplary assays for transcription through the NRB response element may be used or routinely the through the NRB response element that may be used or routinely element activity of polyperdies of the invention (including ambodies and agonists or antigonists of the invention (including ambodies and agonists or amagenists of the invention includes assays disclosed in Berger et al., Gene 66:1-10 (1998). | asthma, allergy, hypersentativity resections, and inflammation. Preferent indications include searchos, and inflammation. Preferent indications include infection (e.g., an infections disease insection (e.g., an infections diseases), immunological disorders, and inflammatory and inflammatory disorders (e.g., as described below flammatory districtly, and "Hindo-Related Disorders"). Preferred inficiations include autoimment diseases (e.g., thermanoid arthritis, systemic lupus experiments of arthritis, systemic lupus arthritis, systemic lupus arthritis, systemic lupus and/or as described below) and immunodeficiencies (e.g., as described below). |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | referred embodinents of the invention include using polypepides of the invention for ambidois; a manufacture of a manufacture of a manufacture of a manufacture of a salma, allergy, hypersensitivity and inflammation.                                                                                                                  |
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| Henthorn et al., Proc Neal, Acad Sci<br>USA 85:642-6346 (1988), Valle<br>Bhaquec et al. Immunology<br>90,455-640 (1997), Aramburau et<br>al., 1 Exp Med 82(2):801-6310 (1995),<br>1 | Seases Apoptosis are well known in<br>caspasse apoptosis are well known in<br>and are and may be used or nominely<br>modified to assess he shifty of<br>polypeptides of the invention<br>to including ambients and agoniss or<br>antagoniss to the invention) to<br>applied espaces protected and<br>apoptosis in immune cells (such as, |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Regulation of apoptosis of immune cells (such as mast cells).                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 550                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HMSJU68                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 146                                                                                                                                                                                                                                                                                                                                      |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | A highly preferred embodiment of |
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| cells are found in connective and mouses litels, must cells, met found in connective and and their activation via and their activation via and their activation via and their activation via monosed litesace tongeton the activation of allergo disease. Degraphisms of allergo disease. Degraphisms of allergo disease. Degraphisms of allergo disease. Degraphisms of any and the surveal. Exempling assays for croatmed y modified to test capase suppossions and meas cell manor survival. Exempling assays for croatmed y modified to test capase or proposions activity induced by polypeptides of the invention of real angenities of the invention) included or meladuling ambidies and againsts of the invention) included and allegal (Chem. 274(28)) 254(07-216).  al. J. Biol Chem. 274(28), 258(01) 260(1). The action of all J. Biol Chem. 274(28), 258(1995), the contents of cash of which are been useff according to these assays are useff according to these assays are discording to these assays and encountered is othered. Exempliary manner cells that may be tasted according to these assays and channer on the little. | Kinase assay. Kinase assays, for |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Activation of Skeletal           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 550                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HMSJU68                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                  |

| the invention includes a method for increasing muscle cell survival An alternative highly preferred embediment of the invention includes a method for decreasing muscle cell survival. A preferred             | includes a method for invention includes a method for stimulating managed cell proliferation. In an aspect of proliferation, In a specific embodiment, skeled a muscle cell proliferation is stimulated. An attentive lightly preferred embodiment of the invention embodiment of the invention misside cell proliferation. In a muscle cell proliferation, in a                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | early cambinary skeleta muscle cell positivations in hishing. A profession of the positivation of the positivation of the invention includes a nethod for attention includes a nethod for attention includes a nethod for attention muscle cell differentiation is a specific of embodiment, skeletal muscle cell comboliment of the invention alternative highly preferred alternative highly preferred and alternative highly preferred in reached for inhibiting includes a method for inhibiting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | and supplied that the special control of the special combodiment, skeletal muscle of differentiation is infinited of differentiation is infinited. If disorders of the musculoskeletal disorders of the musculoskeletal system or Preferred indications include mephasic diseases (e.g., secretable blow under executed blow under secretable disorders blowders). If yep-moliferative Disorders is, disordered blow decentred for decentred blooders disorders (e.g., secretable blow under disorders).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| example an GSK-3 kinase assay, for P13 kinase signal transduction that regulate glucose metabolism and cell survivial are well-known in the art and may be used or routinely modified to assess the ability of | oppophedics or the invention of including authorities and agonists or authorities and agonists or promote or inhibit glucose metabolism and cell survival.  Textuplar associa for PIS himse administrative for the promote or inhibit glucose metabolism and cell survival.  Textuplar associa for PIS himse-inhibit and political to test De Tanton-inhibit of test De Rimse-induced activity that may be used to routinely and remaining the propagation of the properties of the activity of polypophedics of the activity of polypophedics of the control of the properties of the polypophedics of the polypophe | restriction (including antibodies and<br>agonists or antagonists or the<br>agonists or antagonists or the<br>Ferrer et al. Biol Chem 3796,<br>91,100-1110 (1998), Misculina et<br>al., Dabetes 49(2),26,271 (2000),<br>and Sdrucyer et al., Dishore,<br>and Sdrucyer et al., Dishore,<br>and Sdrucyer et al., Dishore,<br>and Sdrucyer et al., Dishore,<br>of each or Wukha tue brent<br>of each or Wukha tue brent<br>or each or Wukha tue Brent<br>entropy. But a proposition of the<br>entropy and proposition of the<br>entropy and proposition of the<br>entropy and proposition of the proposition of<br>entropy and proposition of the proposition of the<br>entropy and proposition of the proposition of the<br>entropy and proposition of the proposition of the<br>entropy and the proposition of the proposition of the<br>entropy and the proposition of the proposition of the<br>entropy and the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the<br>entropy and the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the pr | to the sub-activity of these assays are publicly available (e.g., through the ACCO <sup>P</sup> ). Exemplarly att unpoblast cells that may be used according to the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activity of the activ |
| Mucle Cell P13 Kinase<br>Signalling Pathway                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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| 146                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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| Diso   | Disorders"), neural disorders (e.g., as                          |
|--------|------------------------------------------------------------------|
| Acti   | described below under Incural Activity and Neurological          |
| Dise   | Diseases"), blood disorders (e.g., as                            |
| desc   | described below under "Immune<br>Activity", "Cardiovascular      |
| Diso   | Disorders", and/or "Blood-Related                                |
| Diso   | Disorders"), immune disorders (e.g.,                             |
| as de  | as described below under "Immune                                 |
| Acti   | Activity"), and infection (e.g., as                              |
| desc   | õ                                                                |
| Stru   | Disease"). A nignty preterred<br>indication is disheres mallitus |
| Ans    | An additional highly preferred                                   |
| indic  | indication is a complication                                     |
| asso   | associated with diabetes (e.g.,                                  |
| diab   | diabetic retinopathy, diabetic                                   |
| l neph | nephropathy, kidney disease (e.g.,                               |
| rena   | renal failure, nephropathy and/or                                |
| othe   | other diseases and disorders as                                  |
| desc   | described in the "Renal Disorders"                               |
| secti  | section below), diabetic neuropathy,                             |
| nerv   | nerve disease and nerve damage (e.g,                             |
| due    | due to diabetic neuropathy), blood                               |
| vess   | vessel blockage, heart disease,                                  |
| strok  | stroke, impotence (e.g., due to                                  |
| diab   | diabetic neuropathy or blood vessel                              |
| bloc   | blockage), seizures, mental                                      |
| conf   | confusion, drowsiness, nonketotic                                |
| hype   | hyperglycemic-hyperosmolar coma,                                 |
| card   | cardiovascular disease (e.g., heart                              |
| disea  | disease, atherosclerosis,                                        |
| micr   | microvascular disease, hypertension,                             |
| strok  | stroke, and other diseases and                                   |
| disor  | disorders as described in the                                    |
| "Car   | "Cardiovascular Disorders" section                               |
| olar.  | balour) ductinidamia andoorina                                   |

| disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infections (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's | contracture). An additional | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | indications are disorders of the | musculoskeletal system including | myopathies, muscular dystrophy, | and/or as described herein. | Additional highly preferred | indications include: myopathy, | atrophy, congestive heart failure, | cachexia, myxomas, fibromas, | congenital cardiovascular | abnormalities, heart disease, cardiac | arrest, heart valve disease, and | vascular disease. Highly | preferred indications include | neoplasms and cancer, such as, | rhabdomyoma, rhabdosarcoma, | stomach, esophageal, prostate, and |
|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|----------------------------------|--------------------------------------|------------------------------|-------------------------------------|----------------------------------------|---------------------------------|-----------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|----------------------------------|---------------------------------|-----------------------------|-----------------------------|--------------------------------|------------------------------------|------------------------------|---------------------------|---------------------------------------|----------------------------------|--------------------------|-------------------------------|--------------------------------|-----------------------------|------------------------------------|
|                                |                               |                            |                                        |                                     |                                  |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                  |                                 |                             |                             |                                |                                    |                              |                           |                                       |                                  |                          |                               |                                |                             |                                    |
|                                |                               |                            |                                        |                                     |                                  |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                  |                                 |                             |                             |                                |                                    |                              |                           |                                       |                                  |                          |                               |                                |                             |                                    |
|                                |                               |                            |                                        |                                     |                                  |                                      |                              |                                     |                                        |                                 |                             |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                  |                                 |                             |                             |                                |                                    |                              |                           |                                       |                                  |                          |                               |                                |                             |                                    |

| urinary cancer. Preferred indications also include breast, lung, colon, pancratic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and per-neophastic conditions, such as, hyperplassia, metaplassia, and or dysplassia. | asthma, allegly preferred influentions include asthma, allegge, laypersensitivity precedents and influentation. Preferred influention include disease as described below under "linection disease," immunological disorders, influention processes," immunological disorders, influention and influention processes," immunological disorders, influention disorders (e.g., and described below under "linear Artisty", and "Brood-Related Disorders"), and "Brood-Related Disorders", and "Brood-Related Disorders", and "Brood-Related Disorders", and autoimmunol diseases (e.g., as experted influentions include autoimmunodelicitorics (e.g., as described below).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                                                                                                                                                                                                                                                                         | transcription through the NFRB<br>response electron are well-known in the art and may be used or muited by the confidence of the invention of polyperpickees of the invention to polyperpickees of the invention to regulate NFRB transcription factors and appropriate of the invention to regulate NFRB transcription factors and appropriate of the invention to regulate NFRB transcription factors are appropriated by the propriate of the invention of the propriate of the invention of the propriate of the invention of the propriate of the invention of the polyperpicke of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention include usasy a factor of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention o |
|                                                                                                                                                                                                                                                                         | Activation of Termscription through through Next Seyonse cells (such as EOL I cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                                                                                         | 147 HMTB136                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| are heroit incorporated by reference in a feature in control. For example, a reporter assay (which measures in remarkers of the and a reporter assay (which measures in features in transcription inducible from a NHSA responsive dement in EO.1. ceils) may his the NHSB are sponsive dement in EO.1. ceils) may his the NHSB transcription factor, which is turgenglated by condens, which is turgenglated by condens which in the NHSB transcription factor, which is turgenglated by condens and other factors. Exemple to the NHSB transcription factor, which is turgenglated by condens and of the factors and of the factors and the threat of the transport of costs popular. Easienghils said as the turnum EO.1. cell into or costs popular in the allegage crossnoses; they are recruited to responses of the stage allegate reaction. Easier is and mediate the inflammunory reaction. Easier is and mediate the inflammunory reaction. Easier is and easier in the allegage allegate reaction. Easier is and easier in the allegage and legate crossnose of the stage allegate reaction. Easier is and easier in the allegage and legate crossnose of the stage allegate reaction. Easier is and easier in the allegage and legate controlled to the stage and legate reaction. Easier is and easier in the allegate and legate in the allegate and legate in the allegate and legate in the allegate and legate | Kimes usey, Kinsee sessy, for the invention includes a method for example an GSK-3 lanese sessy, for the invention includes a method for the plantage gluoses methodism and cell alternative lightly preferred survivial are well-known in the art and rank to used or routinely modified to used or toutinely modified to use of the invention or polypoptics of the invention or includes a method for estimation and cell survival. A preferred managemists of the invention in purpose of the invention in combing and cell survival. A preferred promote or highly geness of the invention or includes a method for similarity and cell survival. A preferred promote or highly genesses of the invention or includes a method for inhibiting modified to test P13 kinses-induced includes a method for inhibiting |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 155                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HMTBi36                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 147                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

|  | asso | associated with diabetes (e.g.,        |
|--|------|----------------------------------------|
|  | diat | diabetic retinopathy, diabetic         |
|  | nep  | nephropathy, kidney disease (e.g.,     |
|  | rens | renal failure, nephropathy and/or      |
|  | othe | other diseases and disorders as        |
|  | desc | described in the "Renal Disorders"     |
|  | sect | section below), diabetic neuropathy,   |
|  | ner  | nerve disease and nerve damage (e.g,   |
|  | due  | due to diabetic neuropathy), blood     |
|  | VCSS | vessel blockage, heart disease,        |
|  | stro | stroke, impotence (e.g., due to        |
|  | diah | diabetic neuropathy or blood vessel    |
|  | bloc | blockage), seizures, mental            |
|  | con  | confusion, drowsiness, nonketotic      |
|  | hyp  | hyperglycemic-hyperosmolar coma,       |
|  | carc | cardiovascular disease (e.g., heart    |
|  | disc | disease, atherosclerosis,              |
|  | mic  | microvascular disease, hypertension,   |
|  | orts | stroke, and other diseases and         |
|  | diso | disorders as described in the          |
|  | 2    | "Cardiovascular Disorders" section     |
|  | bele | below), dyslipidemia, endocrine        |
|  | diso | disorders (as described in the         |
|  | "En  | "Endocrine Disorders" section          |
|  | belc | below), neuropathy, vision             |
|  | dini | impairment (e.g., diabetic retinopathy |
|  | and  | and blindness), ulcers and impaired    |
|  | nom  | wound healing, infections (e.g.,       |
|  | infe | infectious diseases and disorders as   |
|  | desc | described in the "Infectious           |
|  | Disc | Diseases" section below, especially    |
|  | oft  | of the urinary tract and skin), carpal |
|  | tunt | tunnel syndrome and Dupuytren's        |
|  | con  | contracture). An additional            |
|  | high | highly preferred indication is obesity |
|  | and  | and/or complications associated with   |
|  | ope  | obesity. Additional highly preferred   |

|     |         |     |                        |                                       | indications include weight loss or     |
|-----|---------|-----|------------------------|---------------------------------------|----------------------------------------|
|     |         |     |                        |                                       | alternatively weight gain              |
|     |         |     |                        |                                       | Additional highly preferred            |
|     |         |     |                        |                                       | indications are complications          |
|     |         |     |                        |                                       | associated with insulin resistance.    |
|     |         |     |                        |                                       | Additional highly preferred            |
|     |         |     |                        |                                       | indications are disorders of the       |
|     |         |     |                        |                                       | musculoskeletal system including       |
|     |         |     |                        |                                       | myopathics, muscular dystrophy,        |
|     |         |     |                        |                                       | and/or as described herein.            |
|     |         |     |                        |                                       | Additional highly preferred            |
|     |         |     |                        |                                       | indications include: myopathy,         |
|     |         |     |                        |                                       | atrophy, congestive heart failure,     |
|     |         |     |                        |                                       | cachexia, myxomas, fibromas,           |
|     |         |     |                        |                                       | congenital cardiovascular              |
|     |         |     |                        |                                       | abnormalities, heart disease, cardiac  |
|     |         |     |                        |                                       | arrest, heart valve disease, and       |
|     |         |     |                        |                                       | vascular disease. Highly               |
|     |         |     |                        |                                       | preferred indications include          |
|     |         |     |                        |                                       | neoplasms and cancer, such as,         |
|     |         |     |                        |                                       | rhabdomyoma, rhabdosarcoma,            |
|     |         |     |                        |                                       | stomach, esophageal, prostate, and     |
|     |         |     |                        |                                       | urinary cancer. Preferred indications  |
|     |         |     |                        |                                       | also include breast, lung, colon,      |
|     |         |     |                        |                                       | pancreatic, brain, and liver cancer.   |
|     |         |     |                        |                                       | Other preferred indications include    |
|     |         |     |                        |                                       | benign dysproliferative disorders and  |
|     |         |     |                        |                                       | pre-neoplastic conditions, such as,    |
|     |         |     |                        |                                       | hyperplasia, metaplasia, and/or        |
|     |         |     |                        |                                       | dysplasia.                             |
|     | HMVBS81 | 552 | Stimulation of insulin | Assays for measuring secretion of     | A highly preferred indication is       |
| 148 |         |     | secretion from         | insulin are well-known in the art and | diabetes mellitus. An                  |
|     |         |     | pancreatic beta cells. | may be used or routinely modified to  | additional highly preferred indication |
|     |         |     |                        | assess the ability of polypeptides of | is a complication associated with      |
|     |         |     |                        | the invention (including antibodies   | diabetes (e.g., diabetic retinopathy,  |
|     |         |     |                        | and agonists or antagonists of the    | diabetic nephropathy, kidney disease   |
|     |         |     |                        | invention) to stimulate insulin       | (e.g., renal failure, nephropathy      |

| secretion. For example, insulin                  | : insulin        | and/or other diseases and disorders as |
|--------------------------------------------------|------------------|----------------------------------------|
| secretion is measured by FMAT                    | v FMAT           | described in the "Renal Disorders"     |
| using anti-rat insulin antibodies.               | ntibodies.       | section below), diabetic neuropathy,   |
| Insulin secretion from pancreatic beta           | pancreatic beta  | nerve disease and nerve damage         |
| cells is upregulated by glucose and              | glucose and      | (e.g., due to diabetic neuropathy),    |
| also by certain proteins/peptides, and           | /peptides, and   | blood vessel blockage, heart disease,  |
| disregulation is a key component in              | component in     | stroke, impotence (e.g., due to        |
| diabetes. Exemplary assays that may              | ssays that may   | diabetic neuropathy or blood vessel    |
| be used or routinely modified to test            | odified to test  | blockage), seizures, mental            |
| for stimulation of insulin secretion             | in secretion     | confusion, drowsiness, nonketotic      |
| (from pancreatic cells) by                       | by               | hyperglycemic-hyperosmolar coma,       |
| polypeptides of the invention                    | cntion           | cardiovascular disease (e.g., heart    |
| (including antibodies and agonists or            | nd agonists or   | disease, atherosclerosis,              |
| antagonists of the invention) include            | ntion) include   | microvascular disease, hypertension,   |
| assays disclosed in: Ahren, B., et al.,          | nen, B., et al., | stroke, and other diseases and         |
| Am J Physiol, 277(4 Pt 2):R959-66                | t 2):R959-66     | disorders as described in the          |
| (1999); Li, M., et al., Endocrinology,           | indocrinology,   | "Cardiovascular Disorders" section     |
| 138(9):3735-40 (1997); Kim, K.H.,                | ; Kim, K.H.,     | below), dyslipidemia, endocrine        |
| et al., FEBS Lett, 377(2):237-9                  | 2):237-9         | disorders (as described in the         |
| (1995); and, Miraglia S et. al.,                 | ct. al.,         | "Endocrine Disorders" section          |
| Journal of Biomolecular Screening,               | ar Screening,    | below), neuropathy, vision             |
| 4:193-204 (1999), the contents of                | contents of      | impairment (e.g., diabetic retinopathy |
| each of which is herein incorporated             | incorporated     | and blindness), ulcers and impaired    |
| by reference in its entirety.                    | rety.            | wound healing, and infection (e.g.,    |
| Pancreatic cells that may be used                | ay be used       | infectious diseases and disorders as   |
| according to these assays are publicly           | ys are publicly  | described in the "Infectious           |
| available (e.g., through the ATCC <sup>M</sup> ) | the ATCCTM)      | Diseases" section below, especially    |
| and/or may be routinely generated.               | y generated.     | of the urinary tract and skin), carpal |
| Exemplary pancreatic cells that may              | cells that may   | tunnel syndrome and Dupuytren's        |
| be used according to these assays                | tese assays      | contracture). An additional            |
| include rat INS-1 cells. INS-1 cells             | . INS-1 cells    | highly preferred indication is obesity |
| are a semi-adherent cell line                    | ll line          | and/or complications associated with   |
| established from cells isolated from             | isolated from    | obesity. Additional highly preferred   |
| an X-ray induced rat transplantable              | ansplantable     | indications include weight loss or     |
| insulinoma. These cells retain                   | ls retain        | alternatively, weight gain.            |
| characteristics typical of native                | of native        | Aditional highly preferred             |
| pancreatic beta cells including                  | cluding          | indications are complications          |

| associated with insulin resistance.                                                        | A highly preferred indication is disheves reclinic.  An additional highly preferred indication is disheves reclinic.  An additional highly preferred indication in disheves (e.g., dishefur entimopathly dative disease) and dishedre a complication associated with dishedre to entimopathly adding dishedres as dishedres as med stored as a described in the 'Renal Dishedres as described in the 'Renal Dishedres as described in the 'Renal Dishedres as described in the 'Renal Dishedres as described in the 'Renal Dishedres as described in the 'Renal Dishedres as dishedre neuropathly, holod vessel blockeg, heart disease, stanke, importore (e.g., the to dishedre neuropath) or blood vessel blockegs, per stankers, montone (e.g., the to dishedre neuropathy or blood vessel blockegs, per stankers, montone) or stankers, montoned countries, disease, ipperenticing to stankers, and other diseases to mortivosal transfers as disease, ibperenting strucks, and other diseases and the other diseases and disorders' section behavy, despitionalist, end derived restriction (e.g., infections diseases and disorders as described in the 'Lincionia and hinchesis and infection (e.g., infections diseases and disorders as electrices diseases and disorders as electrical diseases. |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167. | Assays for measuring secretion of maining well-working and and and and and and and and and and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                            | Simulation of insulin<br>secretion from<br>pancreair beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                            | 523                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                            | HMWDC28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                            | 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| the the turning treat and skin), empall turned syndrome and Dagoytsen's construction. An additional highly preferred indication is obesity and or complications associated with one of the complication in highly preferred indications include weight loss or addrown flounds weight loss or addrown flounds weight gain. Addrown flagibly preferred indications are complications as exociated with instillin resistance.                                                                                                                                              | diabetes mellitus. Additional highly preferred and indication is in preferred indications include complications enclose the encircled and includes associated with diabetes registrate and calabetes registrate and diabetes (e.g., circula fallute, rephropathy, kidney disease (e.g., renal fallute, rephropathy sidney disease (e.g., renal fallute, rephropathy merve diseases and diseathes and diseathed in the 'Renal Disabetes and diseathed was called to the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the c |
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| Exemplary puncratic clientinely generated. Exemplary puncratic cells that may be used according to these assays include at INSF. cells. Nest cells are are a semi-adherent cell line cashifished from cells isolated from any X-ray induced for transpiration and X-ray induced for transpiration and X-ray induced for transpiration and X-ray induced for transpiration characteristics typical of native practice for cells including characteristics typical of native glucose inducible insulin secretion. Helectrones, Asid in et al. Inducerinology 1992 1301 67. | transacription through the DMEF!  Transacription through the DMEF!  Transacription through the DMEF!  The standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the standard and the st |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | transaription vii<br>Phall response<br>Della lesponse<br>element in adipocytes<br>and pre-adipocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 554<br>4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HMWFT65                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 120                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     | HNEEE24 | 555 | Insulin Secretion | Assavs for measuring secretion of      | A highly preferred indication is       |
|-----|---------|-----|-------------------|----------------------------------------|----------------------------------------|
| 151 |         |     |                   | insulin are well-known in the art and  | diabetes mellitus. An additional       |
|     |         |     |                   | may be used or routinely modified to   | highly preferred indication is a       |
|     |         |     |                   | assess the ability of polypeptides of  | complication associated with           |
|     |         |     |                   | the invention (including antibodies    | diabetes (e.g., diabetic retinopathy,  |
|     |         |     |                   | and agonists or antagonists of the     | diabetic nephropathy, kidney disease   |
|     |         |     |                   | invention) to stimulate insulin        | (e.g., renal failure, nephropathy      |
|     |         |     |                   | secretion. For example, insulin        | and/or other diseases and disorders as |
|     |         |     |                   | secretion is measured by FMAT          | described in the "Renal Disorders"     |
|     |         |     |                   | using anti-rat insulin antibodies.     | section below), diabetic neuropathy,   |
|     |         |     |                   | Insulin secretion from pancreatic beta | nerve disease and nerve damage         |
|     |         |     |                   | cells is upregulated by glucose and    | (e.g., due to diabetic neuropathy),    |
|     |         |     |                   | also by certain proteins/peptides, and | blood vessel blockage, heart disease,  |
|     |         |     |                   | disregulation is a key component in    | stroke, impotence (e.g., due to        |
|     |         |     |                   | diabetes. Exemplary assays that may    | diabetic neuropathy or blood vessel    |
|     |         |     |                   | be used or routinely modified to test  | blockage), seizures, mental            |
|     |         |     |                   | for stimulation of insulin secretion   | confusion, drowsiness, nonketotic      |
|     |         |     |                   | (from pancreatic cells) by             | hyperglycemic-hyperosmolar coma,       |
|     |         |     |                   | polypeptides of the invention          | cardiovascular disease (e.g., heart    |
|     |         |     |                   | (including antibodies and agonists or  | disease, atherosclerosis,              |
|     |         |     |                   | antagonists of the invention) include  | microvascular disease, hypertension,   |
|     |         |     |                   | assays disclosed in: Shimizu, H., et   | stroke, and other diseases and         |
|     |         |     |                   | al., Endocr J, 47(3):261-9 (2000);     | disorders as described in the          |
|     |         |     |                   | Salapatek, A.M., et al., Mol           | "Cardiovascular Disorders" section     |
|     |         |     |                   | Endocrinol, 13(8):1305-17 (1999);      | below), dyslipidemia, endocrine        |
|     |         |     |                   | Filipsson, K., et al., Ann N Y Acad    | disorders (as described in the         |
|     |         |     |                   | Sci, 865:441-4 (1998); Olson, L.K.,    | "Endocrine Disorders" section          |
|     |         |     |                   | et al., J Biol Chem, 271(28):16544-    | below), neuropathy, vision             |
|     |         |     |                   | 52 (1996); and, Miraglia S et. al.,    | impairment (e.g., diabetic retinopathy |
|     |         |     |                   | Journal of Biomolecular Screening,     | and blindness), ulcers and impaired    |
|     |         |     |                   | 4:193-204 (1999), the contents of      | wound healing, and infection (e.g.,    |
|     |         |     |                   | each of which is herein incorporated   | infectious diseases and disorders as   |
|     |         |     |                   | by reference in its entirety.          | described in the "Infectious           |
|     |         |     |                   | Pancreatic cells that may be used      | Discases" section below, especially    |
|     |         |     |                   | according to these assays are publicly | of the urinary tract and skin), carpal |
|     |         |     |                   | available (e.g., through the ATCCTM)   | me a                                   |
|     |         |     |                   | and/or may be routinely generated.     | contracture). An additional            |

| highly preferred indication is obesity above complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional alternatively, weight gain. Additional highly preferred indications are complications associated with instilling resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | highly preferred indication is in this preferred indication lightly preferred indications include complications associated with deferred indications include complications associated with difference (e.g. delabeit extenopathy diabetic schophopathy, leitore in repriporative and control for a road influence and diseated as a diseased in the "Rean I Disoatede" and office of the "Rean I Disoatede" associated in the "Rean I Disoatede" associated in the "Rean I Disoatede" associated in the "Rean I Disoatede" associated in the "Rean I Disoatede" associated in the "Rean I Disoatedee and the "Rean I Disoatedee and the "Rean I Disoatedee and the "Rean I Disoatedee and the "Rean I Disoatedee and the "Rean I Disoatedee and the "Rean I Disoatedee and disoated in company or blood vessel blookings, heartures, mental confusion, drowsiness, montal confusion, drowsiness, montal confusion, drowsiness, to prefer and consultations and advanced and disease, degreen and prevention.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Exemplary pancreatic cells that may be used according to these sassys madueet upitating to these sassys and adherent opitatin cells. HITT15 cells. HITT15 and adherent opitatin cell the sabblished from Syrian humster risket cells transformed with SV40. These cells express gluegon, someostatin, and glueoconfooth repeated respirations of the secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret insulin, which is secret in an interventional or secret in the secret in the secret in the secret in the secret in the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret of the secret in the secret of the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secret in the secre | expansis for the regulation of ransarchiou through the DMET propose element are well-known in the rat and many be used or routinely according to a season of the property of the polyperptides of the invention of polyperptides of the invention of polyperptides of the invention of an amagonists of the invention of the polyperptides of the invention of an amagonists of the invention of a season of the polyperptides and agont is such or temporary of the polyperptides and agont of an amagonist of the polyperptides and appropriate the polyperptides and appropriate the production. The DMET response cleaners it proceeds in the GLUT4 promoter and brids to MEE? The promoter and brids to MEE? The measur-prior factor and another transacription factor that is required expression in skeletal nancele. Callut is the primary insulin responsive gluose transporter in far                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transcription via fragilition of transcription via fragilition of transcription via fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragilities of the fragi |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HNFC43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 152                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| stroke, and other diseases and      | disorders as described in the | "Cardiovascular Disorders" section  | below), dyslipidemia, endocrine     | disorders (as described in the     | "Endocrine Disorders" section       | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious      | Diseases" section below, especially | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications    | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly preferred | indications are complications  | associated with insulin resistance. |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |                                  |                                |                             |                                      |                                       |
|-------------------------------------|-------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|----------------------------------------|------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------|-----------------------------|----------------------------------------|--------------------------------------|------------------------------------|----------------------------------|---------------------------------------|------------------------------------|----------------------------------|--------------------------------|-----------------------------|--------------------------------------|---------------------------------------|
| and muscle tissue. Exemplary assays | that may be used or routinely | modified to test for DMEF1 response | element activity (in adipocytes and | pre-adipocytes) by polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed    | inThai, M.V., et al., J Biol Chem,  | 273(23):14285-92 (1998); Mora, S.,  | et al., J Biol Chem, 275(21):16323-8 | (2000); Liu, M.L., et al., J Biol | Chem, 269(45):28514-21 (1994);      | "Identification of a 30-base pair  | regulatory element and novel DNA       | binding protein that regulates the | human GLUT4 promoter in             | transgenic mice", J Biol Chem. 2000  | Aug 4;275(31):23666-73; Berger, et   | al., Gene 66:1-10 (1988); and,    | Cullen, B., et al., Methods in | Enzymol. 216:362-368 (1992), the    | contents of each of which is herein | incorporated by reference in its | entirety. Adipocytes and pre- | adipocytes that may be used | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary cells that may be used | according to these assays include the | mouse 3T3-L1 cell line which is an | adherent mouse preadipocyte cell | line. Mouse 3T3-L1 cells are a | continuous substrain of 3T3 | fibroblasts developed through clonal | isolation. These cells undergo a pre- |
|                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |                                  |                                |                             |                                      |                                       |
| _                                   |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |                                    |                                  |                                |                             |                                      |                                       |

|                                                                                                  | high preferred includions include austima, allegy, massocyonosis (a rare-precedence) and and an electrogeneous disorder characterized by excessive accumulation of mass characterized by excessive accumulation of mass action in the skin, central nervous sustem, and other organis). Preferred indications also include below indications also include below under "Infections (eg., as described below under "Infections Diseases"), infection (eg., as described below under "Infections Diseases"), autoimmune diseases (eg., as described below under "Infections (ig., as described below), autoimmune diseases (eg., as described below), and immunodeficiencies (eg., as described below), and immunodeficiencies (eg., as described below), and immunodeficiencies (eg., as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| adipocyte to adipose-like conversion<br>under appropriate differentiation<br>culture conditions. | increases of decreases) of vibility of any any so that the capacity of clear in the order of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of the capacity of t |
|                                                                                                  | Prolifection of immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                  | 55 <b>6</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                  | HNFFCQ43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                  | 251                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                                                                                                    | reperted infactors include the refrest of infactors include the water of infactors of e.g. as described by wander "Ipportunisticative of Diseasers (e.g., as described by wander "Ipportunisticative of Statistical Diseasers"). In John of the Activity" Cardiorionscular Diseasers, and or "Blood-Related Diseasers", and or "Blood-Related Diseasers", and or "Blood-Related Diseasers", and or "Blood-Related Diseasers", and or "Blood-Related Diseasers, and or "Blood-Related Diseasers", and or "Blood-Related Diseasers (e.g., an infaction) despending and arthrifts, systemic lupus perferred arthrifts, systemic lupus perferred arthrifts, systemic lupus and or sa described below) and immunodeficiencies (e.g., see all and arthrifts, systemic lupus described below). Additional lightly preferred diseasers (e.g., letkenia, lymphoma, and or sa described below under "Hyportyoliferative Diseasers"). "Hyportyoliferative Diseasers (e.g., letkenia, lymphoma, prostate, bereas, lung, colon, puncreatic, described ben'ign in diseasers for diseasers and entracy, sander diseasers and entracy, sander diseasers and entracy, sander diseasers for diseasers and entracy and entrany cancer. Other preferred diseasers functive diseasers and entracy sander of the preferred diseasers functive diseasers and entrany cancer. Other preferred diseasers functive diseasers and entrany cancer.                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| immature human mast cell line established from the peripheral blood of a patient with mast cell leukema, and exhibits many characteristics of immature mast cells. | assays for gignal transduction that assays for gignal transduction that assays for gignal transduction that assays for gignal transduction that and may be used or routinely of modified to seaso such a fully of individual and help of polypeptides of the invention) to polypeptides of the invention) to polypeptides of the invention) to polypeptides of the invention) to polypeptides of the invention) to managonisis to the invention, and analogousis. Reculply seasys for an analogousis are the polypeptides of the invention include that and p38 kinnes activity that may b8 kinnes activity that may b8 kinnes activity that may b8 kinnes induced activity for and p38 kinnes induced activity for and p38 kinnes activity that may b8 kinnes induced activity for the p10 kpp-gdides of the invention include the assays disclosed in Forert et al. (1988), Gipped at 1Exp Cell Ros (1988), Gipped at 1Exp Cell Ros (1989), Chang and Karin, Maure (1986), Chang and Karin, Maure (1999), Chang and Karin, Maure (1999), Chang and Karin, Maure (1994), Chang and Karin, Maure (1995), Chang and Karin, Maure (1994), Chang and Karin, Maure (1995), Chang and Karin, Mau |
|                                                                                                                                                                    | Activation of T-Cell 1938 or INK Signating Pathway.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                    | 536                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                    | HNFC43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                    | 152                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| stroke, impotence (e.g., due to                                           | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and       | disorders as described in the      | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the      | "Endocrine Disorders" section       | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious  | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's      | contracture). An additional        | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. Additional | highly preferred indications are   | complications associated with insulin | resistance.                       |                                 |                                    |                                   |                                 |                                   |
|---------------------------------------------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|----------------------------------------|--------------------------------------|------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|----------------------------------------|------------------------------------|---------------------------------------|-----------------------------------|---------------------------------|------------------------------------|-----------------------------------|---------------------------------|-----------------------------------|
| disregulation is a key component in<br>diabetee Evermlary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000); | Salapatek, A.M., et al., Mol       | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S et. al.,    | Journal of Biomolecular Screening,  | 4:193-204 (1999), the contents of   | each of which is herein incorporated | by reference in its entirety. | Pancreatic cells that may be used   | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary pancreatic cells that may    | be used according to these assays    | include HITT15 Cells. HITT15 are     | an adherent epithelial cell line   | established from Syrian hamster islet  | cells transformed with SV40. These | cells express glucagon, somatostatin, | and glucocorticoid receptors. The | cells secrete insulin, which is | stimulated by glucose and glucagon | and suppressed by somatostatin or | glucocorticoids. ATTC# CRL-1777 | Refs: Lord and Ashcroft. Biochem. |
|                                                                           |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |
|                                                                           |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |
|                                                                           |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |                                   |

|                                                                                        | A highly preferred indication is diabetes mellins. Additional highly preferred indications include complications associated with diabetes (c.g., diabetic retinopathy,             | diabetic nephropathy, kidney disease<br>(e.g., rental failure, nephropathy<br>and/or other diseases and disorders as<br>described in the "Renal Disorders"<br>section belowy, diabetic neuropathy,<br>nerve disease and nerve damage | (e.g., due to diabetic neuropathy),<br>blood vessel blockage, heart disease,<br>stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel<br>blockage), seizures, mental | continuou, drowanness, nonkeciote<br>hyperglycemic-hyperosmolar coma,<br>eardiovascular disease (e.g., heart<br>disease, atherosedenosis,<br>microvascular disease, hypertension,<br>suroke, and other diseases and<br>disorders as described in the | "Cardiovascular Josofters' section<br>below), distiliatemia, endocrine<br>disorders (as described in the<br>"Endocrine Disorders' section<br>below), neuropathy, vision<br>impariment (e.g., diabetic retinopathy<br>and blindress), uleers and impaired<br>wound healing, and infection (e.g.,                | infectious diseases and disorders as<br>described in the "Infectious<br>Diseases" section below, especially |
|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| J. 219: 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | Assays for the regulation of<br>transcription through the DMEF1<br>response element are well-known in<br>the art and may be used or routinely<br>modified to assess the ability of | polypeptides of the invention (including anti-backs and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the CLUT4                                  | promoter) and to regulate insulin<br>production. The DMFFI response<br>element is present in the GLUT4<br>promoter and binds to MEF2<br>transcription factor and another              | transcription factor that is required for insulin regulation of Glud- ocypession in skeletal muscle. (CLUT4 is the primary insulin- responsive gluose transporter in fat  and muscle tissue. Exemplary assays  that may be used or routinely         | modified to lest for DMLH response<br>element activity (in adipocytes and<br>pre-adipocytes) by polypeptides of<br>the invention (including antibodies<br>and agentist or antagonists of the<br>invention) include assays disclosed<br>in That, M.V., et al., J Biol Chem.<br>777(23);1428-92 (1998); Mons, S. | et al., J Biol Chem, 275(21):16323-8<br>(2000); Liu, M.L., et al., J Biol<br>Chem, 269(45):28514-21 (1994); |
|                                                                                        | Regulation of<br>transcription via<br>DMEF1 response<br>element in adipocytes<br>and pre-adipocytes                                                                                |                                                                                                                                                                                                                                      |                                                                                                                                                                                       |                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                |                                                                                                             |
|                                                                                        | 559                                                                                                                                                                                |                                                                                                                                                                                                                                      |                                                                                                                                                                                       |                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                |                                                                                                             |
|                                                                                        | HNFJF07                                                                                                                                                                            |                                                                                                                                                                                                                                      |                                                                                                                                                                                       |                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                | _                                                                                                           |
|                                                                                        | 155                                                                                                                                                                                |                                                                                                                                                                                                                                      |                                                                                                                                                                                       |                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                |                                                                                                             |

| the through treat and skin). An additional highly preferred indications in design as seen design with the preferred indications in session as seed and with obesity. Additional associated with obesity. Additional highly preferred indications include weight lass or alternatively, weight weight lass or alternatively, weight weight lass or alternatively. weight and additional paighty preferred indications are complications associated with insufin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | tallight pretzered industation is datherers realitins. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopality, telatory discusser (e.g., teral failure, rephropality, telatory discusser (e.g., teral failure, rephropality, and/or other discusses and disorders as described in the Venen Disorders's section below), diabetic neuronality.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| regulatory chernett and novel DNA challettilection of a 3th Osseg pair regulatory chernett and novel DNA challed grotein that regulates the human (1.174 promoter in 2000 Aug 4.275 (31) 23664-73. Blot Chem. 2000 Aug 4.275 (31) 23664-73. Blot Chem. 2000 Aug 4.275 (31) 23664-73. Blot Chem. 2000 Aug 4.275 (31) 23664-73. Blot Chem. 2000 Aug 4.275 (31) 23664-73. Blot Chem. 2000 Aug 4.275 (32) 364 (39). He controls of each of which is herein incorporated by reference in its incorporated by reference in its incorporated by reference in its incorporated by reference in its outprovince and the control of the chem. 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32) and 30 (32 | Assays for the regulation of vitability and proliferation of cells in vitro are well-known in the art and may be well-known in the art and may be under or rountinely modified to assess the ability of polypeptides of the invention (including antibodies and agoniss or antagoniss of the invention) to regulate vibality and invention) to regulate vibality and invention) to regulate vibality and invention to regulate vibality and regulated to regulate vibality and regulated to the control of the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cell river-cite for research in the cel |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 559                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| A preferred embodiment of the          | Assays for the activation of                             | Activation of | 559 | HNFJF07 |  |
|----------------------------------------|----------------------------------------------------------|---------------|-----|---------|--|
| resistance.                            | Kelerences: Asiari et al.<br>Endocrinology 1992 130:167. |               |     |         |  |
| complications associated with insulin  | glucose inducible insulin secretion.                     |               |     |         |  |
| highly preferred indications are       | native pancreatic beta cells including                   |               |     |         |  |
| alternatively, weight gain. Additional | cells retain characteristics typical of                  |               |     |         |  |
| indications include weight loss or     | transplantable insulinoma. These                         |               |     |         |  |
| obesity. Additional highly preferred   | from an X-ray induced rat                                |               |     |         |  |
| complications associated with          | line established from cells isolated                     |               |     |         |  |
| preferred indication is obesity and/or | INS-1 cells are a semi-adherent cell                     |               |     |         |  |
| contracture). An additional highly     | these assays include rat INS-1 cells.                    |               |     |         |  |
| tunnel syndrome and Dupuytren's        | cells that may be used according to                      |               |     |         |  |
| of the urinary tract and skin), carpal | generated. Exemplary pancreatic                          |               |     |         |  |
| Diseases" section below, especially    | ATCCTM) and/or may be routinely                          |               |     |         |  |
| described in the "Infectious           | publicly available (e.g., through the                    |               |     |         |  |
| infectious diseases and disorders as   | be used according to these assays are                    |               |     |         |  |
| wound healing, and infection (e.g.,    | its entirety. Pancreatic cells that may                  |               |     |         |  |
| and blindness) ulcers and impaired     | herein incomorated by reference in                       |               |     |         |  |
| immainment (a.g. dishatio setinomethy) | 1996 Jul 10,273(26),17771=9 (1996),                      |               |     |         |  |
| "Endocrine Disorders" section          | (1998); Hugi SK, et al., J Biol Chem                     |               |     |         |  |
| disorders (as described in the         | Endocrinology, 139(4):1494-9                             |               |     |         |  |
| below), dyslipidemia, endocrine        | (2001); Huotari MA, et al.,                              |               |     |         |  |
| "Cardiovascular Disorders" section     | et al., Mol Endocrinol, 15(1):136-48                     |               |     |         |  |
| disorders as described in the          | assays disclosed in: Friedrichsen BN,                    |               |     |         |  |
| stroke, and other diseases and         | antagonists of the invention) include                    |               |     |         |  |
| microvascular disease, hypertension,   | (including antibodies and agonists or                    |               |     |         |  |
| disease, atherosclerosis,              | by polypeptides of the invention                         |               |     |         |  |
| cardiovascular disease (e.g., heart    | proliferation of pancreatic beta cells                   |               |     |         |  |
| hyperglycemic-hyperosmolar coma,       | regulation of viability and                              |               |     |         |  |
| confusion, drowsiness, nonketotic      | used or routinely modified to test                       |               |     |         |  |
| blockage), seizures, mental            | cells. Exemplary assays that may be                      |               |     |         |  |
| diabetic neuropathy or blood vessel    | presence of metabolically active                         |               |     |         |  |
| stroke, impotence (e.g., due to        | the ATP present which signals the                        |               |     |         |  |
| blood vessel blockage, heart disease,  | in culture based on quantitation of                      |               |     |         |  |
| (e.g., due to diabetic neuropathy),    | measures the number of viable cells                      |               |     |         |  |
| nerve disease and nerve damage         | luminescent cell viability assay                         |               |     |         |  |
|                                        |                                                          |               |     |         |  |

| invention includes a method for<br>inhibiting (e.g., reducing) TNF alpha<br>producion. An alternative preferred<br>embodiment of the invention<br>includes a method for stimulating | eg., increasing DNF appla<br>production. Preferred indications<br>include blood dissorders (e.g., as<br>described below under "Immune<br>Artivity", "Blood-Related<br>Bosterles", and "C'ardivosacular<br>Dissorders", and "C'ardivosacular<br>Dissorders", Highly preferred<br>indications include autoimmune<br>viscose (e.g. rheumanda arthritis                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and patients with thermunoid arthritis, An additional highly preferred indication is segais. Highly preferred indications include norphissio diseases (e.g., Latkemia, hyphoran, and on se described below under "Hyperpositientive below under "Hyperpositientive below under "Hyperpositientive preferred indications include norphisms and cancers, such as, for example, latkemia, lymphoma, melanoma, giorne (e.g., milignant melanoma, giorne (e.g., milignant |
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| ranscription through the Serum<br>Response Element (SRE) are well-<br>known in the art and may be used or<br>routinely modified to assess the<br>ability of polypeptides of the     | wenton (including antibodies and agoniss or antagoniss or antagoniss of the invention) to regulate the serum response fetors and modulate the expression of genes involved in expression of genes involved in transcription through the SRI fat transcription through the SRI fat that was be used or maintainly modified to less SRI activity of the polynomials. | of the invention (including authobids and agonists or antigonists of the mention (including authobids of the law mention) include assays tisclenced in Barger et al., Gane 66;1-10 (1998); Cullera and Mahm. Methods in Represe at al., Proc Natl Acad Sci 18 (1992); Ass 56:345-646 (1983); and Hanhorn et al., Proc Natl Acad Sci 18 (1987), the contem of care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (1997), the care to IT (19 | reference in its criticity. Teells that<br>may be used according to these<br>assays are publicly available (e.g.,<br>through the ATCO <sup>20</sup> ). Exemplary<br>mouse Teells that may be used<br>according to these assays include the<br>CTLL cell line, which is an ILL2<br>dependent asspension culture of T<br>cells with cytotoxic activity.                                                                                                                |
| transcription through<br>serum response element<br>in immune cells (such<br>as T-cells).                                                                                            |                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| 155                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Simulation of insulin secretion from pancreatic beta cells. | price proprieta de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control de la control | Assays for measuring severeton of minimum are well-known in the art and may be used or routinely modified to assess the ability of popypatics of the invention (including authodies of additional highly preferred indication assessited with the invention (including authodies of the invention of the invention) to simulate insulin accretion. For example, insulin and/or other diseases and disorders as |
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|                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                |
| I IZ                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 559 559                                                                                                                                                                                                                                                                                                                                                                                                        |

|                                    | _                                      | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., |                                   | -                                      | Diseases" section below, especially  | of the urinary tract and skin), carpal | me a                                | contracture). An additional       | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or  | alternatively, weight gain.    | Aditional highly preferred        | indications are complications   | associated with insulin resistance.  |
|------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|-----------------------------------|---------------------------------|--------------------------------------|
| using anti-rat insulin antibodies. | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S et. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | are a semi-adherent cell line        | established from cells isolated from | an X-ray induced rat transplantable | insulinoma. These cells retain | characteristics typical of native | pancreatic beta cells including | glucose inducible insulin secretion. |
|                                    |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                   |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 |                                      |
|                                    |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                   |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 |                                      |

|                             | A highly preferred embodiment    | of the invention includes a method | for stimulating adipocyte             | proliferation. An alternative highly  | preferred embodiment of the          | invention includes a method for      | inhibiting adipocyte proliferation. | A highly preferred embodiment of    | the invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention           | includes a method for inhibiting     | adipocyte differentiation. A      | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below |
|-----------------------------|----------------------------------|------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|---------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|
| Endocrinology 1992 130:167. | Kinase assay. Kinase assays, for | example an Elk-1 kinase assay, for | ERK signal transduction that regulate | cell proliferation or differentiation | are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the  | invention (including antibodies and | agonists or antagonists of the      | invention) to promote or inhibit cell  | proliferation, activation, and  | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodics and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      |
|                             | Activation of                    | Adipocyte ERK                      | Signaling Pathway                     |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |
|                             | 260                              |                                    |                                       |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |
|                             | HNGDJ72                          |                                    |                                       |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |
|                             |                                  | 156                                |                                       |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |

| include 3173-L1 cells. 373-L1 is an adversar most perdapoye cell into that is a continuous substant of 131 fibroblas cells developed through charal isolation and undergod through charal isolation and undergod a pro-adipoye to adipose-like convexion under the convexion under apportant of differentiation conditions known in the art. | under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune             |                                                                     | _                               | under "Neural Activity and   | infection (e.g. as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------|------------------------------|------------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|
|                                                                                                                                                                                                                                                                                                                                              | include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of | 3T3 fibroblast cells developed through clonal isolation and undergo | a pre-adipocyte to adipose-like | conversion under appropriate | the art                            | ulc alt.                     |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |
|                                                                                                                                                                                                                                                                                                                                              |                                                                                                            |                                                                     |                                 |                              |                                    |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |
|                                                                                                                                                                                                                                                                                                                                              |                                                                                                            |                                                                     |                                 |                              |                                    |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |

| - |  | below), neuropathy, vision              |
|---|--|-----------------------------------------|
|   |  | immairment (e.g., diabetic retinonathy  |
|   |  | and blindness), ulcers and impaired     |
|   |  | wound healing, infection (e.g.,         |
|   |  | infectious diseases and disorders as    |
|   |  | described in the "Infectious            |
|   |  | Diseases" section below (particularly   |
|   |  | of the urinary tract and skin). An      |
|   |  | additional highly preferred indication  |
|   |  | is obesity and/or complications         |
|   |  | associated with obesity. Additional     |
|   |  | highly preferred indications include    |
|   |  | weight loss or alternatively, weight    |
|   |  | gain. Additional highly                 |
|   |  | preferred indications are               |
|   |  | complications associated with insulin   |
|   |  | resistance. Additional highly           |
|   |  | preferred indications are disorders of  |
|   |  | the musculoskeletal systems             |
|   |  | including myopathies, muscular          |
|   |  | Š,                                      |
|   |  | herein. Additional highly               |
|   |  | preferred indications include,          |
|   |  | hypertension, coronary artery           |
|   |  | disease, dyslipidemia, gallstones,      |
|   |  | osteoarthritis, degenerative arthritis, |
|   |  | eating disorders, fibrosis, cachexia,   |
|   |  | and kidney diseases or disorders.       |
|   |  | Preferred indications include           |
|   |  | neoplasms and cancer, such as,          |
|   |  | lymphoma, leukemia and breast,          |
|   |  | colon, and kidney cancer. Additional    |
|   |  | preferred indications include           |
|   |  | melanoma, prostate, lung,               |
|   |  | pancreatic, esophageal, stomach,        |
|   |  | brain, liver, and urinary cancer.       |
|   |  | Highly preferred indications include    |

| lipomas and pivosaromas. Other pre-ferred indications include benign dysproliferative disorders and pre-reophastic conditions, such as, for example, hypothisia, metaplasia, and/ or systhasia. | Verbined by T  In II. 4  In II. 4  In II. 4  In II. 4  In II. 5  I |
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|                                                                                                                                                                                                 | Production of IL-6   IL-6 is sync and production of IL-6 is and has storn get fire cells and has storn get fire cells. IL-6 practicities in richard [4] production (14) April monosal immunition flow opposition and producted by a dispervation flow opposition and production of a monosal invention (Induduit and invention) in mediate invention (Induduit and invention) in mediate invention (Induduit and invention) in mediate invention and modification and differentiation and modification and function Everpheny passoy that up estimination and modification and function and modification and function and modification and function Everpheny passoy that up estimination and modification and supplication and supplication and supplication and function are simulation and simulation and modification and supplication  |
|                                                                                                                                                                                                 | 990                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                 | 156 HNGD772                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|         |     |               | sugasy that may be used or routirely<br>modified to test immunomodulatory<br>and diffreentiation activity of<br>oppophedes of the invention) high<br>oppophedes of the invention) include<br>anamonists of the invention) include<br>assays disclosed in Miraglia et al., I<br>Bondoclark excerning 4:193-<br>204(1999); Rowland et al.,<br>"Lymphocyses, a practical approach"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | allergy, Highly preferred indications include neoplastic diseases (e.g., myeloma, presmeyorana, talekemia, myeloma, presmeyorana, talekemia, myeloma, presmeyorana, talekemia, priparbona, medioma, andor as described below under Highly preferred indications include neoplastus and caneres, such as, myeloma, plasmacytoma, talekemia, lympkora, neclaroma, and prostate, lympkora, neclaroma, and prostate.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|         |     |               | Chargasel et al. Ji mannoi et al. Grabasel et al. Ji mannoi ol cach ol which are bretin is or cach ol which are bretin is curriery. Human dendritic cells that entriety. Human dendritic cells that may be used according to these assays may be isolated using to the entriety as a series of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the | esophagael, stomand, benin, liver and unique and unique oneser. Other preferred indications include bening a special feet and pre-proposition conditions, such as, for example, hypophasia, metaphasia, anetaphasia, anetaphasia, preferred indications include anemia, paracytopenia, letakopenia, thrombodytopenia, Hodgdin si dinombodytopenia, Hodgdin si dinombodytopenia, Hodgdin si discus, caule pinhodyti earmin (ALL), untique myeloma, Burkiti's, Allys, prophora, artifulie myeloma, Burkiti's, Allys, artifulionaria discusse inflammatoxy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| HWGD172 | 945 | Production of | activities.  MIP. Jaloha FMAT Assuss for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | lewerd diseases, septisis, neutropenin, article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article article articl |

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| of the invention includes a method | for stimulating MIP1a production.     | An alternative highly preferred | embodiment of the invention    | includes a method for inhibiting (e.g., | reducing) MIP1a production. A | highly preferred indication is    | infection (e.g., an infectious disease | as described below under "Infectious  | Disease"). Preferred indications | include blood disorders (e.g., as | described below under "Immune     | Activity", "Blood-Related         | Disorders", and/or "Cardiovascular | Disorders"). Highly preferred      | indications include autoimmune     | diseases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,        | multiple sclerosis and/or as described | below) and immunodeficiencies (e.g., | as described below). Additional | highly preferred indications include | inflammation and inflammatory   | disorders. Preferred indications    |                                | _                                      | Hodgkin's disease, acute        | lymphocytic anemia (ALL),  | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory  | bowel disease, sepsis, neutropenia, | neutrophilia, psoriasis, suppression | of immune reactions to transplanted     | organs and tissues, hemophilia,   | _                                      | endocarditis, meningitis, Lyme      |
| immunomodulatory profeins          | produced by activated dendritic cells | that upregulate                 | monocyte/macrophage and T cell | chemotaxis are well known in the art    | and may be used or routinely  | modified to assess the ability of | polypeptides of the invention          | (including antibodies and agonists or | antagonists of the invention) to | mediate immunomodulation,         | modulate chemotaxis, and modulate | T cell differentiation. Exemplary | assays that test for               | immunomodulatory proteins evaluate | the production of chemokines, such | as macrophage inflammatory protein    | 1 alpha (MIP-1a), and the activation | of monocytes/macrophages and T         | cells. Such assays that may be used  | or routinely modified to test   | immunomodulatory and chemotaxis      | activity of polypeptides of the | invention (including antibodies and | agonists or antagonists of the | invention) include assays disclosed in | Miraglia et al., J Biomolecular | Screening 4:193-204(1999); | Rowland et al., "Lymphocytes: a  | practical approach" Chapter 6:138-   | 160 (2000); Satthaporn and Eremin, J | R Coll Surg Ednb 45(1):9-19 (2001); | Drakes et al., Transp Immunol        | 8(1):17-29 (2000); Verhasselt et al., J | Immunol 158:2919-2925 (1997); and | Nardelli et al., J Leukoc Biol 65:822- | 828 (1999), the contents of each of |
| MIPIalpha                          | 1                                     |                                 |                                |                                         |                               |                                   |                                        |                                       |                                  |                                   |                                   |                                   |                                    |                                    |                                    |                                       |                                      |                                        |                                      |                                 |                                      |                                 |                                     |                                |                                        |                                 |                            |                                  |                                      |                                      |                                     |                                      |                                         |                                   |                                        |                                     |
|                                    |                                       |                                 |                                |                                         |                               |                                   |                                        |                                       |                                  |                                   |                                   |                                   |                                    |                                    |                                    |                                       |                                      |                                        |                                      |                                 |                                      |                                 |                                     |                                |                                        |                                 |                            |                                  |                                      |                                      |                                     |                                      |                                         |                                   |                                        |                                     |
| 156                                |                                       |                                 |                                |                                         |                               |                                   |                                        |                                       |                                  |                                   |                                   |                                   |                                    |                                    |                                    |                                       |                                      |                                        |                                      |                                 |                                      |                                 |                                     |                                |                                        |                                 |                            |                                  |                                      |                                      |                                     |                                      |                                         |                                   |                                        |                                     |

| Disease, asthma, and alletgy. Peterved indications also include morphistic diseases (e.g., leukernie, mythoma, and ora seesribed below under "Hyperproliferative Disorders"). Highly preferred Disorders"). Highly preferred Disorders"). Highly preferred Disorders", highly preferred cencers, such as, leukernia, coulon, paracretiic, essephigeal, colon, paracretiic, essephigeal, colon, paracretiic, essephigeal cencer. Other preferred indications include benign dysproliferative include benign dysproliferative conditions, such as, for example, onditions, such as, for example, dysplasia, medapiasia, and or | A highly perforded enchodiment of the invention includes a method for inhibiting (e.g., decreasing) TNF and inhibiting (e.g., decreasing) TNF and inhibiting (e.g., decreasing) TNF and perioducion And alternative highly perfected embodiment of the sturnation includes a method for sturnation include (e.g., increasing) TNF and alternation include blood disorders of e.g. as described below under "Himmune Activity" "Blood-Related indications include blood disorders "and or" Cardiovascular Disorders" and or" Cardiovascular indications include autorimment indications include autorimment indications include autorimment seases (e.g., incluminod autorimment seases (e.g., incluminod effectives in mitiple selectoris and/or as described below). Bostings 1 Testl.                                                                                                                                                              |
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| which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques dischool herein or otherwise known in the art. Human dendritic cells are anigen presenting cells in suspension presenting cells in suspension presenting cells in suspension and authorities and or cytokines, infinite and upregulate T cell proliferation and functional activities.                                                                                                                                                                         | The PAMT. Assays for immunoandalinoty proteins produced by activated macorphages, etc. [1,6], firothesias, sanoth massle, and other cell types that exert a wide water of inflammatory and colouxie effects on a variety of inflammatory and rate of monitorial mine art and may be used or routinely medited to assay agonists or magaonists of the invention (including antihodies and agonists or an appearation) to meditare immunoandalisticm, modulate immunoandalisticm, modulate immunoandalisticm, modulate immunoandalisticm, modulate immunoandalisticm, modulate the production of cytokines such as the production of cytokines such as the immunoandalisticm, modulate the production of cytokines such as the modulation of cytokines such as the immuneancediation of cytokines such as the immuneancediation of cytokines such as the induction or inhibition of an different adjust (TIVEa), and the induction or inhibition of an |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Production of TNF alpha by dendritic cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 095                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HNGD/72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| mediated immune response, and       | suppressing a T cell-mediated   | immune response. Additional highly | preferred indications include | inflammation and inflammatory | disorders, and treating joint damage  | in patients with rheumatoid arthritis. | An additional highly preferred         | indication is sepsis. Highly  | preferred indications include | neoplastic diseases (e.g., leukemia, | lymphoma, and/or as described | below under "Hyperproliferative  | Disorders"). Additionally, highly  | preferred indications include   | neoplasms and cancers, such as,      | leukemia, lymphoma, melanoma,      | glioma (e.g., malignant glioma), | solid tumors, and prostate, breast,   | lung, colon, pancreatic, esophageal, | stomach, brain, liver and urinary      | cancer. Other preferred indications | include benign dysproliferative | disorders and pre-neoplastic   | conditions, such as, for example, | hyperplasia, metaplasia, and/or        | dysplasia. Preferred indications    | include anemia, pancytopenia,    | leukopenia, thrombocytopenia,        | Hodgkin's disease, acute          | lymphocytic anemia (ALL), | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, neutropenia, | neutrophilia, psoriasis, suppression | of immune reactions to transplanted |
|-------------------------------------|---------------------------------|------------------------------------|-------------------------------|-------------------------------|---------------------------------------|----------------------------------------|----------------------------------------|-------------------------------|-------------------------------|--------------------------------------|-------------------------------|----------------------------------|------------------------------------|---------------------------------|--------------------------------------|------------------------------------|----------------------------------|---------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------|-----------------------------------|----------------------------------------|-------------------------------------|----------------------------------|--------------------------------------|-----------------------------------|---------------------------|----------------------------------|--------------------------------------|-------------------------------------|-----------------------------|--------------------------------------|-------------------------------------|
| inflammatory or cytotoxic response. | Such assays that may be used or | routinely modified to test         | immunomodulatory activity of  | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include  | assays disclosed in Miraglia et al., J | Biomolecular Screening 4:193- | 204(1999); Rowland et al.,    | "Lymphocytes: a practical approach"  | Chapter 6:138-160 (2000);     | Verhasselt et al., Eur J Immunol | 28(11):3886-3890 (1198); Dahlen et | al., J Immunol 160(7):3585-3593 | (1998); Verhasselt et al., J Immunol | 158:2919-2925 (1997); and Nardelli | et al., J Leukoc Biol 65:822-828 | (1999), the contents of each of which | are herein incorporated by reference | in its entirety. Human dendritic cells | that may be used according to these | assays may be isolated using    | techniques disclosed herein or | otherwise known in the art. Human | dendritic cells are antigen presenting | cells in suspension culture, which, | when activated by antigen and/or | cytokines, initiate and upregulate T | cell proliferation and functional | activities.               |                                  |                                      |                                     |                             |                                      |                                     |
|                                     |                                 |                                    |                               |                               |                                       |                                        |                                        |                               |                               |                                      |                               |                                  |                                    |                                 |                                      |                                    |                                  |                                       |                                      |                                        |                                     |                                 |                                |                                   |                                        |                                     |                                  |                                      |                                   |                           |                                  |                                      |                                     |                             |                                      |                                     |
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| hypercoquiation, dishess, hemophilia, hypercoquiation, dishess mellinas, endocardiis, meningits, Lyme Desses, cuedite repetrision injury, and satima and illergy. An additional preferred indication is infection (e.g., an infection disease a deserbed below under "infection Gas, an Disease"). | high preferred indications include inflantantion (cartie and chronic), restroated expension (cartie and chronic), and altergy. Highly perferred indications include inflammatori dash perferred indications include inflammatori dash conferences, inmamological disorders, neoplastic disorders (such as and cardiovascular disorders (such as and cardiovascular disorders (such as and cardiovascular disorders (such as and cardiovascular disorders (such as and cardiovascular disorders). Blood-Related Activity. ** Blood-Related Activity.** Blood-Related indications include neoplasms and recent legit corrioran, and present legit corrioran, and present legit corrioran, and present lang coint puncturic, esoplageal, stomach, brint, liver and indications include being indications include being neoplastic conditions, such as, for example, hyperplastia, metaplisia, and or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|                                                                                                                                                                                                                                                                                                    | handbelled cells which are cells that line blood vessels, and are involved in clinic to megiopersis vesselur into fluidio, but are not iminited to megiopersis vesselur to in incitoson that include, but are not iminited to megiopersis vesselur to medicility vascular tone, and immune cell certwassiston. Exemplary endothelial cells that may be used in ICAM production assays include human umbilical variance and the repression of ICAM (CDS4) as include human umbilical variance available from commercial sources, available from commercial sources, available from commercial sources, available from commercial confict (CAM CDS4) as impergraded by cyclokines or other factors, and ICAM expression is important in mediating immune and endochelial cell interactions leading to immune and inflammatory componers, Assays for measuring expression of ICAM I are well-concluded on ICAM I are well-concluded on ICAM I are well-concluded in seasons that invention (including antipoldess and invention) to regulate ICAM-I are well-invention) to regulate ICAM-I are well invention to regulate ICAM-I are well-invention to regulate ICAM-I are well-invention to regulate ICAM-I are well-invention) to regulate ICAM-I are well invention to regulate ICAM-I are well invention to regulate ICAM-I are well and the breaked or multinely modified to make the reset or multinely undefined in mean than be used or multinely undefined in the bar and or multinely undefined in mean than be used or multinely modified to regulate ICAM-I |
|                                                                                                                                                                                                                                                                                                    | Appropries of ICAM in production of ICAM in production of ICAM in the human turbilical voir endothisis cells (HUVEC)).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                    | 989                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| measure ICAM-1 expression include<br>assay delished in: Rolfo Fig. 4 at,<br>Atheroscherosis, 149(1)99-11.<br>Atheroscherosis, 149(1)99-11.<br>Atheroscherosis, 149(1)99-11.<br>Immunol, 154(9)238-236 (1995)<br>Immunol, 154(9)238-236 (1995)<br>Physiol Lung Cell Mol Physiol,<br>Physiol Lung Cell Mol Physiol,<br>Physiol Lung Cell Mol Physiol,<br>Physiol Lung Cell Mol Physiol,<br>economiss of each of which is here<br>contents of each of which is here<br>enitery. | are well known in the art and may be are well known in the art and may be helpful of prolypticates of the helpful of prolypticates of the invention (including antibedies and againsts or antagenists or the major to regular production are arrangle. How The MAT may be used or example. Part MAT may be used or example. Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Part MAT may be used or example; Or large or the part may be all the part and agoniss or antageniss or the unumlication or endebtic lead its which line versous blood vessels, and are involved in limited to, angiogenesis, vascular more and immune cell carravasation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| restnosis and atherosclerosis.                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| inflammation and secretion of IL-8 may play an important role in recruitment and activation of immune cells such as neutrophils, macrophages, and Jymphocytes. | immunementalistics from The Stays for PARTIES FMAT. Assays for from intubue derivates for Teells, and toolooplist are well monocycs, and toolooplist are well monocycs, and toolooplist are well monocycs, and toolooplist are well known in the art and may be used or the minute you folloop to sessess the ability of polypepules of the immunormediation, induce endeather immunormediation, induce coll-mediated immunity, and the immunity of polypepules of the immunormediated immunity and the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of the stay of th |
|                                                                                                                                                                | Production of RANTES (such as human while as the anotherial cells (HUVEC))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|                                                                                                                                                                | 136                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | inflatibly preferred indications include inflammation (caute and chronic).  Bellich preferred indications include allergy. Highly preferred indications include inflammatory descretes, such as the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the contr |
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| contents of each of which are herein<br>incorporated by reference in its<br>entirety. Endothedial cells that may<br>be used according to these assays are<br>publicly available (e.g., through the<br>ATCCV <sup>3</sup> ). Exemplary exclonebial<br>of bear assays include human unbilied<br>that the each according to<br>these assays include human unbilied<br>that the each according to<br>the each of the each according to<br>the each of the each according to<br>the each of the each according to<br>which are endothedial cells which<br>line venous blood vessels, and are<br>involved in functions that irelade,<br>but are not limited to, angiogenesis,<br>we worked the each each each each each<br>account premedially, yeasalter rose,<br>and immune cell extravasation. | Assays for measuring expression of VCAM are well-known in the art and may be used or runningly medical assess the ability of polypeptides of the invention (including anabodies and agonists or nanaponists of the invention) to regulate VCAM-1 expression. For example, RMAT may be used to meant the approxison, For example, RMAT may be used to meant the expression in endothelial cells are cells that into blood vessels, and are involved in financiate that induction that include, but are not limited to, angiogenesis, vascular more and example vendolish cells that may be used on engalescensis, vascular more well extravession. Exemplary endothelial cells that may be used according to these assays method but mean unbillical vein example of the property of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of the example of  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | behavior of VCAM in endotheinal cells can see human imbilical vein cardotheila cells (HUVEC))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 980                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HNGW72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 156                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| dysproliferative disorders and pre-<br>propriation confusion such as, for<br>example, hyperplasia, metablasia,<br>and/or dysplasia.                                                                                                                                                           | A preferred unbediment of the invention includes a method for invention includes a method for probability (e.g., reducing) TNE alpha probability (e.g., reducing) TNE alpha probability (e.g., reducing) TNE alpha producino An alternative proferred control of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the probability of the |
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| sources. The expression of VCAM (CD106), a membran-associated protein, can be upregulated by cookings on other factors, and contributes to the extravassion of by priphocytes, leuncytes and other immune cells from blood vessels, thus VCAM expression plays as not inflammatory responses. | treassay for the activation of treassay for the activation of treassary for the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the acti |
|                                                                                                                                                                                                                                                                                               | Avariation of transcription through a start response element in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                               | 9,01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                               | HNGE009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                               | 157                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| An additional highly preferred indication is sepsis. Highly preferred indications include          | neoplastic diseases (e.g., leukemia,<br>lhe lymphoma, and/or as described | ۳ ــ                                                               | _                              | neoplasms and cancers, such as, for<br>example, leukemia, lymphoma, | melanoma, glioma (e.g., malignant | glioma), solid tumors, and prostate, | breast, lung, colon, pancreatic, | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia, | pancytopenia, leukopenia, | thrombocytopenia, Hodgkin's | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple | myeloma, burkitt s lympnoma, | disease, inflammatory bowel disease. | neutropenia, neutrophilia, psoriasis, | suppression of immune reactions to | transplanted organs and tissues, | hemophilia, hypercoagulation, | diabetes mellitus, endocarditis, | meningitis, Lyme Disease, cardiac | IO | allergy. An additional preferred |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------|-----------------------------------|--------------------------------------|----------------------------------|---------------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------------|--------------------------------|------------------------------|--------------------------------------|---------------------------------------|------------------------------------|----------------------------------|-------------------------------|----------------------------------|-----------------------------------|----|----------------------------------|
| may be used according to these assays are publicly available (e.g., through the ATCCTM). Exemplary | mouse T cells that may be used according to these assays include the      | CTLL cell line, which is an IL-2 denendent suspension culture of T | cells with cytotoxic activity. |                                                                     |                                   |                                      |                                  |                                 |                            |                                     |                                     |                                   |                             |                             |                           |                             |                                   |                                |                              |                                      |                                       |                                    |                                  |                               |                                  |                                   |    |                                  |
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| infectious disease as described below<br>under "Infectious Disease"). | A highly perferred indication is fleghese meltiliars, An additional lightly perferred indication is a sometime of the perferred indication is a sometime of the perferred indication is a sometime of the perferred indication is a sometime of the perferred indication is a sometime of the perferred indication is a sometime of the perferred indication in a sometime of the perferred indication in the "Ream Disonders" as described in the "Ream Disonders as and searched in the "Ream Disonders as and nerve change of e.g., the total bisonders is merred indication currently and perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perferred in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect in the perfect i |
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|                                                                       | 851                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| and syndrome and Daymyters's contracture). An additional highly preferred indication is obesity and ro-complications associated with obesity. Additional highly preferred indications indicative such weight loss or alternatively, weight gain. Additional highly preferred indications and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Preferred indications include blood disorders (e.g., sa ekseribed below made "Imman, extrivity," "Blood-Redard Disorders," andor "Edwinosaches," andor "Edwinosaches," and so "Edwinosaches Disorders," and infection (e.g., an infection disease infection (e.g., an infection diseases). Preferred indications include automation durities, systemic, justs or edwinosis, multiple sciences (e.g., sa exercibed below), immanuodeliciencies (e.g., sa exercibed helow), mamunodeliciencies (e.g., sa exercibed helow), manuore sesponse, and muntue response, and immune response, and efficional immune response, and efficional immune response, and further distinguish inflammation inflammation inflammation and inflammation and inflammation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| and/or may be routinely teacherd and of may be routinely generated.  Exemplary penceratic cells that may be used according to these assays include HIT15 Cells. HIT15 and and been epithelial cell line established from Syrian harsier sied cells transformed with SV40. These cells transformed with SV40. These cells express gluongon, sammostatin, and glucoordicad receptors. The cells secrete insulia, which is cells secrete insulia, which is cells secrete insulia, which is gluose and gluocodicious. ATC# (KR-1777 and suppressed by contatostatin or glucocontroids. ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (KR-1777 and ATC# (K | Assays for the activation of transacription through the cAMP response element are well-known in the art and may be used or routinely modified to assays the ability of polypeptides of the invention of the activation of the activa |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | transcription (or development of transcription through creaming element in immune cells (such as T-cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| disordens. Highly preferred indisordens. Highly preferred disordens indications include reoplastic diseases (e.g., Intkernia, Jopahona, and ora sedescholer below under "Hyperproliterative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, lenkennia, lymphoma (e.g., Teal lymphoma, Hodgiri's disease). Indiportant indigitative diseases, lymphoma, indiportant prostate, developing include being only marcatic coophingent, someon, breit, liver and urinary someon, parcetaire, esophageal, someon, Deriver and urinary conditions, such as, for example, preparation of the proper last intenditions, and preparation diseases, and many objectived indications include being desproliterative diseases, conditiones, such as, for example, lymphocytica enemia (ALI.) plasmocytoma, multiple myelom, artitle indications in termspirated organic ananyopoma, artitritis, AIDS, granulomatous subjections to transpirated organic and increases, informatous benefit diseases, segus, incumporal, neuroporal, neuroporal, neuroporal, neuroporal, artitritis, AIDS, granulomatous edgesses, informatopatial, activating in Lympe reactions to transpirated organic and placery. | A highly preferred embodiment of<br>the invention includes a method for<br>stimulating (e.g., increasing) MCP-1<br>production. An alternative highly |
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| invention) include resays disclosed in Berger et al., Gene 66:1-10 (1998); Culten and Matin, Methods in Armyon 216:3-5-3-66 (1992); Henthourn et al., Proc Natl Acad Sci (1992); Henthourn et al., Proc Natl Acad Sci (1992); Henthourn et al., Proc Natl Acad Sci (1992); All Sty Sci-3-d-2-66 (1998); Bank et al., Virus Genes 15(2);105-117 Immunol 10(2),659-665 (1998), the entirety. To calls that may be used accounting to these seasys are publicly available (e.g., through the centirety. To calls that may be used according to these seasys are publicly available (e.g., through the CTL cell line, whileh is a suspension culture of ILL edglesis in that may be used according to these ways include the CTL cell line, whileh is a suspension culture of ILL edglesis of dependent cyotoxics T cells.                                                                                                                                                                                                                                                                                                                                                                                                                | MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Production of MCP-1                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 563                                                                                                                                                  |
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| preferred embodiment of the         | invention includes a method for      | inhibiting (e.g., reducing) MCP-1    | production. A highly preferred     | indication is infection (e.g., an   | infectious disease as described below | under "Infectious Disease"). | Additional highly preferred | indications include inflammation and | inflammatory disorders. Preferred | indications include blood disorders | (e.g., as described below under     | "Immune Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"). Highly preferred | indications include autoimmune     | discases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,     | multiple sclerosis and/or as described | below) and immunodeficiencies (e.g., | as described below). Preferred        | indications also include anemia,      | pancytopenia, leukopenia,              | thrombocytopenia, Hodgkin's   | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple      | myeloma, Burkitt's lymphoma, | arthritis, AIDS, granulomatous  | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, | psoriasis, suppression of immune   | reactions to transplanted organs and | tissues, hemophilia,             | hypercoagulation, diabetes mellitus, | endocarditis, meningitis (bacterial | and viral), Lyme Disease, asthma, | and allergy Preferred indications |
| activation of monocytes and T cells | are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the | invention (including antibodies and | agonists or antagonists of the        | invention) to mediate        | immunomodulation, induce    | chemotaxis, and modulate immune      | cell activation. Exemplary assays | that test for immunomodulatory      | proteins evaluate the production of | cell surface markers, such as     | monocyte chemoattractant protein   | (MCP), and the activation of  | monocytes and T cells. Such assays | that may be used or routinely         | modified to test immunomodulatory | and diffferentiation activity of       | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Miraglia et al., J | Biomolecular Screening 4:193- | 204(1999); Rowland et al.,        | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000);    | Satthaporn and Eremin, J R Coll | Surg Ednb 45(1):9-19 (2001); and     | Verhasselt et al., J Immunol       | 158:2919-2925 (1997), the contents | of each of which are herein          | incorporated by reference in its | entirety. Human dendritic cells that | may be used according to these      | assays may be isolated using      | techniques disclosed herein or    |
|                                     |                                      |                                      |                                    |                                     |                                       |                              |                             |                                      |                                   |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   |                                        |                                      |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 |                                      |                                    |                                    |                                      |                                  |                                      |                                     |                                   | _                                 |
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| also include mophastic diseases (e.g., fletterini, lympiona, and or as described below under described below under "Hyperpoliterative Disorders"). Highly preferred indications include mophasms and cancers, such as, fletterini, lympiona, prostaic, bereat, img. colon, panceratic, bereat, img. colon, panceratic, and uniany cancer. Other preferred indications include benign preferred indications include benign and prepopulations conditions, such as, for example, hyporhilasis, areatplasis, areatplasis, areatplasis, areatplasis, and prepared to the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of | A highly preferred indication is diabetes reallins.  A highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, kilney disease (e.g., treal fallure, rephropathy and addition engineably, kilney disease (e.g., treal fallure, rephropathy and or other diseases and diseatores as described in the 'Renal Disoaters' as described in the 'Renal Disoaters' section below), diabetic neuropathy, nerve diseases and nerve damage (e.g., the on diabetic neuropathy, blood vessel blockege, heart disease, canton below), diabetic neuropathy or blood vessel blockege, heart disease, mental blockege), sezures, mental blockege, peart disease, mental blockege, peart disease, mental disease, mental categories, mental disease, mental disease, dispertencient, disease, and disease (e.g., heart disease, and other diseases, hypertencien).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| otherwise known in the art. Human dendric cells are angien presenting cells in asspension culture, which, when activated by antigen and/or cytokines, initiate and tupegulate T ech prolification and inactional activities.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the shifting of polypythids of the invention (including unabodies or the invention) to slimitate insulin securetion. For example, insulin securetion, For example, insulin securetion for example, insulin securetion from pancreatic best and an example, insulin securetion from pancreatic best of the polyperion of the international professional p |
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|     |        |     |                                                                       | The Physiol 2,774 Pt 2),R995-466 (1999); Li, M., et al., Endocrinology, 1993/353-46 (1997); K. M., et al., Endocrinology, 1998/353-46 (1997); K. M., et al., FEBS, Lett. 3,772-94, (1995); and, Miraglin S et al., 1993, and, Miraglin S et al., 1993, and of boundard 10 bounderoules Screening, 4:193-204 (1999), the contents of by reference in its entirely. Paractale cells that may be task of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the pr | "Cardiovascular Disorders' section "Cardiovascular Disorders' section delayout, designificant, andocrine disorders (edsexrhed in the "Endocrine Disorders" section disorders (edsexrhed in the "Indocrine Disorders" section impairment (e.g., diabetit retimopulity and blindress), thouse and impaired wound healing, and infection (e.g., infections diseases and disorders as described in the "Infections and blindress, histories and and contractured.  An additional and properers of contracture). An additional and contracture). An additional infection infection is esociated with obesity. Additional highly preferred infections inductions in decired the discontinuity of the and infections induction is every discontinuity, weight gain. |
|-----|--------|-----|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 159 | HNGJ31 | 563 | Activation of Skeletal<br>Mucle Cell P13 Kinase<br>Signalling Pathway | Michaelmontonia 292 130;167.  Kimae assay, Kimse assay, for example at GNS-Kimse assay, for P13 kimse signal transduction that P13 kimse signal transduction that actual epicone are transduction that actual transduction that and may be used or routinely and may be used or routinely and may be used or routinely and may be used or routinely and may be the invention of the deciding antibodies and agoniss or antigoniss of the invention of underling multibodies and agoniss or antigoniss of the invention to more for inhigh glucose more for inhigh glucose more for inhigh glucose metabolism and cell survivia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly preferred embodiment of the invention inducts a method for increasing muscle cell survival An admentive lightly preferred armative lightly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention of method for simulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation; in a specific embodiment, skeletal muscle cell proliferation; is simulated. An                                                                                                                                                                                                                                                                    |

| Exemplany assays for P13 kinase and vivily that may be used or routinely modified to use P13 kinase-induced and vivily of polyperdics of the invention (including antibodies and anguages) and the invention include assays (sleebed in Forest et al., 1804 Chem 379(6-8) 39,1101-110 (1998), Nisonilane et al. 1010-110 (1998), Nisonilane et al. 2011 (10,110 (1998), Nisonilane et ete et et et et et et et et et et et et et et et et et al. 2011 (10,110 (1998), Nisonilane et ATCCPs). Exemplay et unpoblas et els inter included from primary et et et et al. 2011 (10,110 et lesse assays include [e.e., fluequit the ATCCPs). Exemplay et unpoblas et els inter isolated from primary ettures of rat internat and interso of rat internat and interso of rat internat and interso et and striated from multimatedated rayoubes and striated from multimatedated rayoubes and striated from media. | alternative highly preferred<br>embodiment of the invention<br>includes a method for inhibiting            | muscle cell proliferation. In a<br>specific embodiment, skeletal muscle<br>cell proliferation is inhibited. A | preferred embodiment of the invention includes a method for               | stimulating muscle cell<br>differentiation. In a specific                | embodiment, skeletal muscle cell<br>differentiation is stimulated. An | alternative highly preferred<br>embodiment of the invention     | includes a method for inhibiting      | specific embodiment, skeletal muscle                                          | cell differentiation is inhibited.           | Highly preferred indications include | disorders of the musculoskeletal     | system. Preferred indications       | include teopiasue diseases (e.g., as<br>described below under | "Hyperproliferative Disorders"),     | endocrine disorders (e.g., as           | described below under "Endocrine | Disorders"), neural disorders (e.g., as | Activity and Neurological | Diseases"), blood disorders (e.g., as | described below under "Immune | Activity", "Cardiovascular | Disorders", and/or "Blood-Related | Disorders"), immune disorders (e.g., | as described below under "Immune | Activity"), and infection (e.g., as | described below under "Infectious |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------------------------------|--------------------------------------|-----------------------------------------|----------------------------------|-----------------------------------------|---------------------------|---------------------------------------|-------------------------------|----------------------------|-----------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-----------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Exemplary assays for P13 kinase activity that may be used or routinely modified to lest P13 kinase-induced | activity of polypeptides of the invention (including antibodies and agonists or antagonists of the            | invention) include assays disclosed in<br>Forrer et al., Biol Chem 379(8- | 9):1101-1110 (1998); Nikoulina et<br>al., Diabetes 49(2):263-271 (2000); | and Schreyer et al., Diabetes<br>48(8):1662-1666 (1999), the contents | of each of which are herein<br>incorporated by reference in its | entirety. Rat myoblast cells that may | be used according to mese assays are<br>publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary rat myoblast | cells that may be used according to  | these assays include L6 cells. L6 is | an adherent rat myoblast cell line, | thick miscle that fises to form                               | multinucleated myotubes and striated | fibers after culture in differentiation | media.                           |                                         |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                            |                                                                                                               |                                                                           |                                                                          |                                                                       |                                                                 |                                       |                                                                               |                                              |                                      |                                      |                                     |                                                               |                                      |                                         |                                  |                                         |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                            |                                                                                                               |                                                                           |                                                                          |                                                                       |                                                                 |                                       |                                                                               |                                              |                                      |                                      |                                     |                                                               |                                      |                                         |                                  |                                         |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |

| - |  | Dispase") A highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|   |  | indication is diabetes mellitus.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|   |  | An additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|   |  | indication is a complication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|   |  | associated with diabetes (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   |  | diabetic retinopathy, diabetic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|   |  | nephropathy, kidney disease (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   |  | renal failure, nephropathy and/or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|   |  | other diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   |  | described in the "Renal Disorders"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   |  | section below), diabetic neuropathy,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|   |  | nerve disease and nerve damage (e.g,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|   |  | due to diabetic neuropathy), blood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   |  | vessel blockage, heart disease,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   |  | stroke, impotence (e.g., due to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   |  | diabetic neuropathy or blood vessel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   |  | blockage), seizures, mental                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|   |  | confusion, drowsiness, nonketotic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|   |  | hyperglycemic-hyperosmolar coma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|   |  | cardiovascular disease (e.g., heart                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   |  | disease, atherosclerosis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|   |  | microvascular disease, hypertension,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|   |  | stroke, and other diseases and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|   |  | disorders as described in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|   |  | "Cardiovascular Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|   |  | below), dyslipidemia, endocrine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|   |  | disorders (as described in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|   |  | "Endocrine Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|   |  | below), neuropathy, vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|   |  | impairment (e.g., diabetic retinopathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|   |  | and blindness), ulcers and impaired                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   |  | wound healing, infections (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|   |  | infectious diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|   |  | described in the "Infectious                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|   |  | Diseases" section below, especially                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|   |  | of the urinary tract and skin), carpal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|   |  | tunnel syndrome and Dupuytren's                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|     |         |     |                    |                                   | contracture). An additional                  |
|-----|---------|-----|--------------------|-----------------------------------|----------------------------------------------|
|     |         |     |                    |                                   | highly preferred indication is obesity       |
|     |         |     |                    |                                   | and/or complications associated with         |
|     |         |     |                    |                                   | obesity. Additional highly preferred         |
|     |         |     |                    |                                   | indications include weight loss or           |
|     |         |     |                    |                                   | alternatively, weight gain.                  |
|     |         |     |                    |                                   | Additional highly preferred                  |
|     |         |     |                    |                                   | indications are complications                |
|     |         |     |                    |                                   | associated with insulin resistance.          |
|     |         |     |                    |                                   | Additional highly preferred                  |
|     |         |     |                    |                                   | indications are disorders of the             |
|     |         |     |                    |                                   | musculoskeletal system including             |
|     |         |     |                    |                                   | myopathies, muscular dystrophy,              |
|     |         |     |                    |                                   | and/or as described herein.                  |
|     |         |     |                    |                                   | Additional highly preferred                  |
|     |         |     |                    |                                   | indications include: myopathy,               |
|     |         |     |                    |                                   | atrophy, congestive heart failure,           |
|     |         |     |                    |                                   | cachexia, myxomas, fibromas,                 |
|     |         |     |                    |                                   | congenital cardiovascular                    |
|     |         |     |                    |                                   | abnormalities, heart disease, cardiac        |
|     |         |     |                    |                                   |                                              |
|     |         |     |                    |                                   | vascular disease. Highly                     |
|     |         |     |                    |                                   | preferred indications include                |
|     |         |     |                    |                                   | neoplasms and cancer, such as,               |
|     |         |     |                    |                                   | rhabdomyoma, rhabdosarcoma,                  |
|     |         |     |                    |                                   | stomach, esophageal, prostate, and           |
|     |         |     |                    |                                   | urinary cancer. Preferred indications        |
|     |         |     |                    |                                   | also include breast, lung, colon,            |
|     |         |     |                    |                                   | pancreatic, brain, and liver cancer.         |
|     |         |     |                    |                                   | Other preferred indications include          |
|     |         |     |                    |                                   | benign dysproliferative disorders and        |
|     |         |     |                    |                                   | pre-neoplastic conditions, such as,          |
|     |         |     |                    |                                   | hyperplasia, metaplasia, and/or<br>dvsnlasia |
|     | HNGJE50 | 564 | Production of IL-6 | IL-6 FMAT. IL-6 is produced by T  | A highly preferred embodiment of             |
| 160 |         |     |                    | cells and has strong effects on B | the invention includes a method for          |
|     |         |     |                    | cells. IL-6 participates in IL-4  | stimulating (e.g., increasing) IL-6          |

|   | 3 -                                    | 3                                     |
|---|----------------------------------------|---------------------------------------|
| _ | induced tgr production and increases   | production. An alternative inginy     |
|   | IgA production (IgA plays a role in    | preferred embodiment of the           |
|   | mucosal immunity). IL-6 induces        | invention includes a method for       |
|   | cytotoxic T cells. Deregulated         | inhibiting (e.g., reducing) IL-6      |
|   | expression of IL-6 has been linked to  | production. A highly preferrred       |
|   | autoimmune disease, plasmacytomas,     | indication is the stimulation or      |
|   | myelomas, and chronic                  | enhancement of mucosal immunity.      |
|   | hyperproliferative diseases. Assays    | Highly preferred indications include  |
|   | for immunomodulatory and               | blood disorders (e.g., as described   |
|   | differentiation factor proteins        | below under "Immune Activity",        |
|   | produced by a large variety of cells   | "Blood-Related Disorders", and/or     |
|   | where the expression level is strongly | "Cardiovascular Disorders"), and      |
|   | regulated by cytokines, growth         | infection (e.g., as described below   |
|   | factors, and hormones are well         | under "Infectious Disease"). Highly   |
|   | known in the art and may be used or    | preferred indications include         |
|   | routinely modified to assess the       | autoimmune diseases (e.g.,            |
|   | ability of polypeptides of the         | rheumatoid arthritis, systemic lupus  |
|   | invention (including antibodies and    | erythematosis, multiple sclerosis     |
|   | agonists or antagonists of the         | and/or as described below) and        |
|   | invention) to mediate                  | immunodeficiencies (e.g., as          |
|   | immunomodulation and                   | described below). Highly preferred    |
|   | differentiation and modulate T cell    | indications also include boosting a B |
|   | proliferation and function.            | cell-mediated immune response and     |
|   | Exemplary assays that test for         | alternatively suppressing a B cell-   |
|   | immunomodulatory proteins evaluate     | mediated immune response. Highly      |
|   | the production of cytokines, such as   | preferred indications include         |
|   | IL-6, and the stimulation and          | inflammation and inflammatory         |
|   | upregulation of T cell proliferation   | disorders.Additional highly preferred |
|   | and functional activities. Such        | indications include asthma and        |
|   | assays that may be used or routinely   | allergy. Highly preferred indications |
|   | modified to test immunomodulatory      | include neoplastic diseases (e.g.,    |
|   | and diffferentiation activity of       | myeloma, plasmacytoma, leukemia,      |
|   | polypeptides of the invention          | lymphoma, melanoma, and/or as         |
|   | (including antibodies and agonists or  | described below under                 |
|   | antagonists of the invention) include  | "Hyperproliferative Disorders").      |
|   | assays disclosed in Miraglia et al., J | Highly preferred indications include  |
|   | Biomolecular Screening 4:193-          | neoplasms and cancers, such as,       |

| 73                                                                                                                                                                                                                 |                                                                                                                                                                                                                                           |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                             | ø                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| myclonna, plasmacytoma, leukemia,<br>lymphoma, melanoma, and prostate,<br>breast, lung, colon, panceadic,<br>esophageal, stomach, brain, liver and<br>uniany cancer. Other preferred<br>indications include benign | dysproliferative disorders and pre-<br>noplastic conditions, such as, for<br>example, hyperplasia, metaplasia,<br>and/or dysplasia. Preferred<br>indications include anemia,<br>pancytopenia, lenkopenia,<br>thrombocytopenia, Hodgkin's  | dusease, acute lymphocytic anorma<br>(ALL), multiple myeloma, Burkitt's<br>lymphoma, arthritis, AIDS,<br>granulonatous disease, inflammatory<br>bowel disease, sepsis, neutropenia, | entuophilia, postivais, suppression<br>of immune reactions to transplanted<br>agrees and fisses, hemophilia,<br>hypercoagulation, diabetes mellitus,<br>endocauditis, meningitis, and Lyme<br>Dessee. An additional preferred<br>indication is infection (e.g., an<br>infection disease as described below<br>mader "Infections Diseases"). | thigh preferred indication is discheres realitins. An additional highly preferred indication is a complication secondicated with discheres (e.g., discheric retinopathy, ickiney discheres (e.g., renal failure, rephropathy, ickiney discheres (e.g., renal failure, rephropathy andie order disenses and disorders as described in the Kenal Disouders's section below, dischere conserved in the Section Polowy, discheric resurpostity, section Polowy, dischere and secretors and section Polowy, dischere the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property o |
| 204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are berein                           | incorporated by reference in its entirely. Human deadrific cells that may be used according to these assays may be isolated using techniques disolosed herein or olderwise known in the art. Human dendritic cells are antigen presenting | cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.                             |                                                                                                                                                                                                                                                                                                                                             | Assays for measuring excertion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including authodics the invention (including authodics of the invention) to stimulate insulin secuetion. For example, insulin secuetion is necessared by IPAAT using anti-art insulin antibodies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                           |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                             | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                           |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                             | 564                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                           |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                             | HNGJE50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                    |                                                                                                                                                                                                                                           |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                             | 160                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| nerve disease and nerve damage (e.g., due to diabetic neuropathy), Mond vascel Mordone heart disease            | broom vesser brockage, treat usease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage) segimes                            | confusion, drowsiness, mental<br>hyperglycemic-hyperosmolar coma,  | cardiovascular disease (e.g., heart<br>disease, atherosclerosis,       | microvascular disease, hypertension, stroke, and other diseases and | disorders as described in the<br>"Cardiovascular Disorders" section | below), dyslipidemia, endocrine<br>disorders (as described in the        | "Endocrine Disorders" section       | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired<br>wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious<br>Diseases" section below, esnecially | of the urinary tract and skin), carpal | mea                                  | contracture). An additional<br>highly preferred indication is obesity  | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | atternativery, weight gain. Additional<br>highly preferred indications are | complications associated with insulin | resistance.                       |                                 |                                    |
|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------|----------------------------------------|----------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------|----------------------------------------|--------------------------------------|------------------------------------------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|----------------------------------------------------------------------------|---------------------------------------|-----------------------------------|---------------------------------|------------------------------------|
| Insulin secretion from pancreatic beta cells is upregulated by glucose and also by cortain proteins honties and | also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or manipular modified to test. | for stimulation of insulin secretion<br>(from pancreatic cells) by | polypeptides of the invention<br>(including antibodies and agonists or | assays disclosed in: Shimizu, H., et                                | al., Endocr J, 47(3):261-9 (2000);<br>Salapatek, A.M., et al., Mol  | Endocrinol, 13(8):1305-17 (1999);<br>Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | 52 (1996); and, Miraglia S et. al.,    | Journal of Biomolecular Screening,<br>4:193-204 (1999), the contents of    | each of which is herein incorporated | by reference in its entirety.  Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be rounnely generated.  Exemplary pancreatic cells that may | be used according to these assays    | include HITT15 Cells. HITT15 are     | an adherent epithelial cell line   | cells transformed with SV40. These                                         | cells express glucagon, somatostatin, | and glucocorticoid receptors. The | cells secrete insulin, which is | stimulated by glucose and glucagon |
|                                                                                                                 |                                                                                                                                                       |                                                                    |                                                                        |                                                                     |                                                                     |                                                                          |                                     |                                        |                                                                            |                                      |                                                                     |                                        |                                      |                                                                        |                                      |                                      |                                    |                                                                            |                                       |                                   |                                 |                                    |
|                                                                                                                 |                                                                                                                                                       |                                                                    |                                                                        |                                                                     |                                                                     |                                                                          |                                     |                                        |                                                                            |                                      |                                                                     |                                        |                                      |                                                                        |                                      |                                      |                                    |                                                                            |                                       |                                   |                                 |                                    |

| HNGND37 S65 | Regulation of                                                   | and suppressed by somatostatin or<br>glucocortivoids. ATTC# CRL-1777<br>Refsi: Lord and Asheroft. Biochem.<br>J. 219: 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | A highly preferred indication is                                                                                   |
|-------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| 600         | regulation of<br>transcription through<br>the PEPCK promoter in | Assays for the regulation of transcription through the PEPCK promoter are well-known in the art                                                                                                      | A mgmy pretered mateauon is<br>diabetes mellitus. An<br>additional highly preferred indication                     |
|             | hepatocytes                                                     | and may be used or routinely<br>modified to assess the ability of<br>polypeptides of the invention                                                                                                   | is a complication associated with<br>diabetes (e.g., diabetic retinopathy,<br>diabetic nephropathy, kidney disease |
|             |                                                                 | (including antibodics and agonists or<br>antagonists of the invention) to<br>activate the PEPCK promoter in a                                                                                        | (e.g., renal failure, nephropathy<br>and/or other diseases and disorders as<br>described in the "Renal Disorders"  |
|             |                                                                 | reporter construct and regulate liver<br>gluconeogenesis. Exemplary assays                                                                                                                           | section below), diabetic neuropathy,<br>nerve disease and nerve damage                                             |
|             |                                                                 | for regulation of transcription<br>through the PEPCK promoter that<br>may be used or routinely modified to                                                                                           | (c.g., due to diabetic neuropainy),<br>blood vessel blockage, heart disease,<br>stroke, impotence (c.g., due to    |
|             |                                                                 | test for PEPCK promoter activity (in<br>hepatocytes) of polypeptides of the                                                                                                                          | diabetic neuropathy or blood vessel<br>blockage), seizures, mental                                                 |
|             |                                                                 | invention (including antibodies and<br>agonists or antagonists of the                                                                                                                                | confusion, drowsiness, nonketotic<br>hyperglycemic-hyperosmolar coma,                                              |
|             |                                                                 | invention) include assays disclosed in<br>Berger et al., Gene 66:1-10 (1998);                                                                                                                        | cardiovascular disease (e.g., heart<br>disease, atherosclerosis,                                                   |
|             |                                                                 | Cullen and Malm, Methods in<br>Enzymol 216:362-368 (1992);                                                                                                                                           | microvascular disease, hypertension,<br>stroke, and other diseases and                                             |
|             |                                                                 | Henthorn et al., Proc Natl Acad Sci<br>USA 85:6342-6346 (1988);                                                                                                                                      | disorders as described in the<br>"Cardiovascular Disorders" section                                                |
|             |                                                                 | Lochhead et al., Diabetes 49(6):896-<br>903 (2000); and Yeagley et al., J Biol                                                                                                                       | below), dyslipidemia, endocrine<br>disorders (as described in the                                                  |
|             |                                                                 | Chem 275(23):17814-17820 (2000),                                                                                                                                                                     | "Endocrine Disorders" section                                                                                      |
|             |                                                                 | herein incorporated by reference in                                                                                                                                                                  | impairment (e.g., diabetic retinopathy                                                                             |
|             |                                                                 | its entirety. Hepatocyte cells that<br>may be used according to these                                                                                                                                | and blindness), ulcers and impaired<br>wound healing, infection (e.g., an                                          |

| sisine<br>le                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | assays are publicly available (e.g., through the ATCCTM) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used | infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the uninary tract and skin), carpal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | amino transferase that is inducible<br>with glucocorticoids, insulin, or                                                                    | highly preferred indication is obesity<br>and/or complications associated with                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Additional highly proferred indecisions are complication seasociated with insulin resist Additional highly proferred indecisions are to complication seasociated with insulin resist Additional highly preferred indecisions are disorders of the immestivenes are disorders of an immestivenes are disorders of the immestivenes are disorders of the indecisions include dystoments and or as described herein. Additional highly preferred indications include glycogen indications include glycogen indications include glycogen disease (e.g. glycogeneses), here paparitis, gallsones, circhosis, hier regarderatis or nextroil disease, an obobile they disease, cystiphotemia and children in the indications of high proferred indications. They below duct "Immune Activ" "Thomas Activ" "Thomas Activ" "Thomas Activ" "Thomas Activ" "Thomas Activ" "Thomas Activ" "Thomas Activ" "Thomas Activity" is in under "Immune Activ" "Thomas Activity" in indications of each activity of indication of each activity of indication of the particular indications of the particular indications of the control indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indications of the particular indication                                               | cAMP derivatives.                                                                                                                           | obesity. Additional highly preferred indications include weight loss or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Additional flighty preferred indications are complication associated with inalian resists associated with inalian resists associated with inalian resists and a second or indications are disorders of in musculosekelat dystomers and indications are disorders of inmissions are disorders of inmissions are disorders of incidential playin preferred indications include glycogen indications include glycogen indications include glycogen indications include glycogen indications include glycogen indications include glycogen indications include glycogen indications include glycogen indications include glycogen indications include glycogen included glycogen in the glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen glycogen                                                |                                                                                                                                             | alternatively, weight gain.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| sussociated with insign resists  Additional highly preferred infectionise are disorders of I mesculoscleda systems in sussection of monosclede and systems in off mesculoscleda systems in additional highly preferred infectionise, mesculo fetter infectionise, mesculo fetter infectionise, mesculo fetter infectionise, mesculo fetter infectionise, mesculo fetter infectionise, mesculo fetter infectionise, and other disease infectionism, and other disease infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and other infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and infectionism, and inferior inferior infectionism, and inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferior inferi                                               |                                                                                                                                             | Additional highly preferred indications are complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Additional mighty peterred indications are desired between the measurement of measurement of measurement of measurement of measurement of measurement of peters of measurement of peters of measurement included protected indications include glyoogen discuss (e.g., glyoogenoses). hepatitis, galistone, circles illustry, degeneration, in discuss cybridgement of measurement of measure                                               |                                                                                                                                             | associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| musualisektela systems ind musualisektela systems ind myopothies, musualiar dysun andor as described herein. Additional highly preferred indicational highly preferred indicational highly preferred indicational highly preferred indicational highly preferred indications include glyosopic libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative or necroil libric digenerative digenerative libric digenerative or necroil libric digenerative digenerative libric digenerative or necroil libric digenerative digenerative libric digenerative or necroil libric digenerative or necroil libric digenerative digenerative libric digenerative digenerative libric digenerative or necroil libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerative libric digenerativ                                               |                                                                                                                                             | Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional figure Additional f |
| myodules, musului dysto<br>and/or as described harein,<br>Additional highly proferred<br>indications include glyogen<br>disease (e.g., glyogenoses),<br>hepatitis, gallstones, carbosi<br>hepatitis, gallstones, carbosi<br>liver, degeneration, in<br>flighty proferred indications<br>flighty proferred indications<br>Highly proferred indications<br>the proferred indications<br>bood disorders (e.g., as described)<br>'Cardiovasculta Disorders',<br>'Thodo Related Disorders',<br>'Thodo Related Disorders',<br>'Thomas Astronomy as described in<br>indee' "Immune Artiv'  Cardiovasculta Disorders',<br>'Thomas Astronomy as described in<br>indee' "Immune Artiv'  Cardiovasculta Disorders',<br>'Thomas Astronomy as described in<br>indee' "Immune Artiv'  Cardiovasculta Disorders',<br>'Thomas Astronomy as described in<br>indee' "Immune Artiv'  Thomas Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as described in the Astronomy as a descri |                                                                                                                                             | musculoskeletal systems including                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| andor as described herein.  Additional highly preferred indications include glyogen discusses (e.g., glyogenoses).  Indications include glyogen discusses (e.g., glyogenoses), hepatitis, galistones, cirrhosi lices according a licenter generation, in the control indication glyogenoses, activities in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the control in the con                                               |                                                                                                                                             | myopathies, muscular dystrophy,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| disease, alcobibli (her disea  fibrosis, liver regeneration, n  disease, deshipichmis and ch  metabolism, and preferred indications  Highly proferred indications  below under "Immune Activ "Cardiovascular Diseaders",  "Thood Related Diseaders",  "Thood Related Diseaders",  diseaders (e.g., as deserted)  diseaders (e.g., as deserted)  diseaders (e.g., as deserted)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                             | hepatius, ganstones, curnosis of the<br>liver, degenerative or necrotic liver                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| fibrosis, liver regueration, in diseases, destinication and dependent and dependent and dependent fibrosis. In disease, despinication and toponication and toponication and toponication. In Highly proferred indications book diseases (e.g., as described). "Cardiovascular Diseases," "Blood disearders", "Blood described bisearders," "Blood described bisearders, disearched indications and described disearchers (e.g., as described indications as described indications as described indications are described indications.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                             | disease, alcoholic liver diseases,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| disease, debiliofamina and chi<br>metabolism, and the paptocard<br>Highly preferred indications<br>the plant of the properties of the properties of the paptocard<br>body under "Immune Active"<br>"Cardiovascular Diseardes",<br>"Though Cardiovascular Diseardes",<br>"Though Cardiovascular Diseardes",<br>diseardes (e.g., as described)<br>indications of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the plant of the pl                    |                                                                                                                                             | fibrosis, liver regeneration, metabolic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| mentolonism, and toperiocard indications  Highly preferred indications  Hodd disorders (e.g., as dess  below under "Immune Active"  "Cardowscalar Disorders,"  "Though Cardowscalar Disorders,"  "Shock Cardowscalar Disorders,"  "Shock Cardowscalar Disorders,"  "Shock Cardowscalar Disorders,"  "Gisorders (e.g., as described) in under "Immune Active"), in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                             | disease, dyslipidemia and cholesterol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| highly better includions hold protect modelulors bood disordes (e.g., se dee bood water "Include Disordes", "Cardiovascular Disordes", "Thomas Active Disordes", "Shood Seckarded Disordes", in the Cardiovascular Disordes", "An includio and the Cardiovascular Disordes, "An includio and the Cardiovascular Disordes," in the Cardiovascular Disordes, "Thromas Actively"), in the Cardiovascular Disordes, "Thromas Actively"), in the Cardiovascular Disordes, "Thromas Actively"), in the Cardiovascular Disordes, "Thromas Actively"), in the Cardiovascular Disordes, "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "Thromas Active Disordes," "T                                               |                                                                                                                                             | metabolism, and hepatocarcinomas.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Pedro under Timmune Acity  "Cardiovascula Disorders,"  "Thook Related Disorders,"  "Blook Related Disorders,"  index (e.g., as deserbed)  index (e.g., as deserbed)  index (e.g., as deserbed)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                             | blood disorders (e.g., as described                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| "Cartionseatula Disorders", "Tolion-Aclated Disorders", "Blood-Related Disorders (e.g., as described i inder "Immume Aclatifu"), in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                             | below under "Immune Activity",                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| "Piloto Related Disarders", "Piloto Related Disarders", disarders (e.g., as described) inunder "Innume Antivity"), in ("Administration Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related Related                                               |                                                                                                                                             | "Cardiovascular Disorders", and/or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| disorders (e.g., as described lunder immune Advisor).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                             | "Blood-Related Disorders"), immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| under "Immune Activity"), ii                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                             | disorders (e.g., as described below                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| as a consistent and an an an an an an an an an an an an an                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                             | under "Immune Activity"), infection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| ו (כיציי מת חתבכתותים מופכים                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                             | (e.g., an infectious disease and/or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| "Intertous pisseuses"), and concrine disorder (e.g., as described below under "indexine"), and muter "indexine"). Basel muter "indexine" Disorders"), and metal disorders (e.g., as described below under "below under "below under "leighe problem (e.g., as described below under "leighe problem (e.g., as described below under "leighen problem (e.g., as described below under "leighen problem (e.g., as described below under "leighen (e.g., as described below under "leighen prostate"). Preferred indexinos include "leighen" (e.g., leighen, lymphom, prostate, letwenin, lymphom, prostate, esophageal, storaet, Other indexions include benign dyspullicative disorders and pre-modplastic conditions, such as, for noophastic conditions, such as, for noophastics, metaplissis, me | A shaye for measuring elettion flux are well-denown in the art and maybe disheson entities are well-denown in the art and maybe disheson entities are well-denown in the art and maybe disheson entities are well-denown in the art and maybe disheson entities are well-denown in the art and maybe disheson entities are somptication sesseriated with the art and maybe disheson entitle and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art and the art art and the art art and the art art and the art art and the art art and the art art and the art art and the art art and the art art and the art art and the art art art and the art art art and the art art art and the art art art art and the art art art art art art art art art art                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                         | 17-11-12                                 |
|-----------------------------------------|------------------------------------------|
| Calcium responsive signamig             | Olochage), scizmes, mental               |
| functions Example a secure that         | bymaralycamic-hymarosmolar coma          |
| amon he wood on continues and iffed to  | condigence of the discount of the second |
| may be used of rounnely modified to     | discussional discase (e.g., near         |
| measure calcium nux by                  | disease, ameroscierosis,                 |
| polypeptides of the invention           | microvascular disease, hypertension,     |
| (including antibodies and agonists or   | stroke, and other diseases and           |
| antagonists of the invention) include   | disorders as described in the            |
| assays disclosed in: Satin LS, et al.,  | "Cardiovascular Disorders" section       |
| Endocrinology, 136(10):4589-601         | below), dyslipidemia, endocrine          |
| (1995);Mogami H, et al.,                | disorders (as described in the           |
| Endocrinology, 136(7):2960-6            | "Endocrine Disorders" section            |
| (1995); Richardson SB, et al.,          | below), neuropathy, vision               |
| Biochem J, 288 ( Pt 3):847-51           | impairment (e.g., diabetic retinopathy   |
| (1992); and, Meats, JE, et al., Cell    | and blindness), ulcers and impaired      |
| Calcium 1989 Nov-Dec;10(8):535-41       | wound healing, and infection (e.g.,      |
| (1989), the contents of each of which   | infectious diseases and disorders as     |
| is herein incorporated by reference in  | described in the "Infectious             |
| its entirety. Pancreatic cells that may | Diseases" section below, especially      |
| be used according to these assays are   | of the urinary tract and skin), carpal   |
| publicly available (e.g., through the   | tunnel syndrome and Dupuytren's          |
| ATCCTM) and/or may be routinely         | contracture). An additional              |
| generated. Exemplary pancreatic         | highly preferred indication is obesity   |
| cells that may be used according to     | and/or complications associated with     |
| these assays include HTT15 Cells.       | obesity. Additional highly preferred     |
| HITT15 are an adherent epithelial       | indications include weight loss or       |
| cell line established from Syrian       | alternatively, weight gain.              |
| hamster islet cells transformed with    | Aditional highly preferred               |
| SV40. These cells express glucagon,     | indications are complications            |
| somatostatin, and glucocorticoid        | associated with insulin resistance.      |
| receptors. The cells secrete insulin,   |                                          |
| which is stimulated by glucose and      |                                          |
| glucagon and suppressed by              |                                          |
| somatostatin or glucocorticoids.        |                                          |
| ATTC# CRL-1777 Refs: Lord and           |                                          |
| Ashcroft. Biochem. J. 219: 547-551;     |                                          |
| Santerre et al. Proc. Natl. Acad. Sci.  |                                          |

|                          | allegy were dreid included allegy and sathma. Additional allegy and sathma. Additional allegy and sathma. Additional included includes include immune and hematopoietic disorders of as a described below under "fumum Activity", and "Blaod-Reidet Dasorders"), autorimmune Reiders Dasorders"), autorimmune Reiders Dasorders (e.g., and "Blaod-Reider Dasorders"), autorimmune systemin lupus expremental entiries, systemin lupus expremental entire services (e.g., as described below), bossing a Technumodeficiencies (e.g., as elemental entire responses, and suppressing a Technediated immune responses, and immune responses.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| USA 78: 4339-4343, 1981. | activation of T-cells are well known in the art and may be used or nothingly the art and may be used or nothingly of polypexides of the maintenty modified to assess the against or polypexides of the invention (including antibodies and againsts or arangentists of the production of T-L0 and/or activation production of T-L0 and/or activation by the area of the invention (including the area of the invention (including antibodies of the invention (including antibodies of the invention) to modulate IL-10 invention) to modulate IL-10 invention to modulate IL-10 invention to modulate IL-10 invention to modulate IL-10 invention of the invention of the invention and the invention of the invention and the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the interaction of T-I2 cells and IL-1. Factors that induce of T-I2 cells and IL-1. Factors that induce of T-I2 cells and IL-1. Factors that induce of T-I2 cells and IL-1. Factors that induce of T-I2 cells and IL-1. Factors that induce of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The intraction of T-I2 cells and II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II-1. The II |
|                          | Production of II10 and activation of T-cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                          | 995                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                          | HNG0I12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                          | 162                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| and styling. Primary 2 helper 2 cells are generated by in vitro culture certain production of the continue of the cells are generated by in vitro culture the polarization conditions susing perplaceral blood tymphocytes cells are cells and the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of | Assays for measuring expression of Highly preferred indications included VCAM are well-known in the art and inflammation (acute and chronic).  may be traced or rountingly authoridised to assass the shifts of polyperpicies of allergy. Highly preferred indications the incention (tocklating authoride and agonists or anagonists or the incention) to regulate VCAM inflammation for part and agonists or entangenists of the inflammation of cell attention of cell atte |
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| initiation and pubagonesis of allergy and ashma. Primary Thelpot<br>cells are generated via in vitro out un<br>under TD2 polarizing conditions<br>uning peripheral blood lymphocytes<br>isolated from cord blood.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | According to VECAM acrostomic copression in anotabelial cells may be used or routingly modificated vicin submain and the investment controlled to the property of the property of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HNHI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|     |         |     |                        | inflammatory responses.                 |                                        |
|-----|---------|-----|------------------------|-----------------------------------------|----------------------------------------|
|     | HNHEU93 | 295 | Stimulation of insulin | Assays for measuring secretion of       | A highly preferred indication is       |
| 163 |         |     | secretion from         | insulin are well-known in the art and   | diabetes mellitus. An                  |
|     |         |     | pancreatic beta cells. | may be used or routinely modified to    | additional highly preferred indication |
|     |         |     |                        | assess the ability of polypeptides of   | is a complication associated with      |
|     |         |     |                        | the invention (including antibodies     | diabetes (e.g., diabetic retinopathy,  |
|     |         |     |                        | and agonists or antagonists of the      | diabetic nephropathy, kidney disease   |
|     |         |     |                        | invention) to stimulate insulin         | (e.g., renal failure, nephropathy      |
|     |         |     |                        | secretion. For example, insulin         | and/or other diseases and disorders as |
|     |         |     |                        | secretion is measured by FMAT           | described in the "Renal Disorders"     |
|     |         |     |                        | using anti-rat insulin antibodies.      | section below), diabetic neuropathy,   |
|     |         |     |                        | Insulin secretion from pancreatic beta  | nerve disease and nerve damage         |
|     |         |     |                        | cells is upregulated by glucose and     | (e.g., due to diabetic neuropathy),    |
|     |         |     |                        | also by certain proteins/peptides, and  | blood vessel blockage, heart disease,  |
|     |         |     |                        | disregulation is a key component in     | stroke, impotence (e.g., due to        |
|     |         |     |                        | diabetes. Exemplary assays that may     | diabetic neuropathy or blood vessel    |
|     |         |     |                        | be used or routinely modified to test   | blockage), seizures, mental            |
|     |         |     |                        | for stimulation of insulin secretion    | confusion, drowsiness, nonketotic      |
|     |         |     |                        | (from pancreatic cells) by              | hyperglycemic-hyperosmolar coma,       |
|     |         |     |                        | polypeptides of the invention           | cardiovascular disease (e.g., heart    |
|     |         |     |                        | (including antibodies and agonists or   | disease, atherosclerosis,              |
|     |         |     |                        | antagonists of the invention) include   | microvascular disease, hypertension,   |
|     |         |     |                        | assays disclosed in: Ahren, B., et al., | stroke, and other diseases and         |
|     |         |     |                        | Am J Physiol, 277(4 Pt 2):R959-66       | disorders as described in the          |
|     |         |     |                        | (1999); Li, M., et al., Endocrinology,  | "Cardiovascular Disorders" section     |
|     |         |     |                        | 138(9):3735-40 (1997); Kim, K.H.,       | below), dyslipidemia, endocrine        |
|     |         |     |                        | et al., FEBS Lett, 377(2):237-9         | disorders (as described in the         |
|     |         |     |                        | (1995); and, Miraglia S ct. al.,        | "Endocrine Disorders" section          |
|     |         |     |                        | Journal of Biomolecular Screening,      | below), neuropathy, vision             |
|     |         |     |                        | 4:193-204 (1999), the contents of       | impairment (e.g., diabetic retinopathy |
|     |         |     |                        | each of which is herein incorporated    | and blindness), ulcers and impaired    |
|     |         |     |                        | by reference in its entirety.           | wound healing, and infection (e.g.,    |
|     |         |     |                        | Pancreatic cells that may be used       | infectious diseases and disorders as   |
|     |         |     |                        | according to these assays are publicly  | described in the "Infectious           |
|     |         |     |                        | available (e.g., through the ATCCTM)    | Diseases" section below, especially    |
|     |         |     |                        | and/or may be routinely generated.      | of the urinary tract and skin), carpal |
|     |         |     |                        | Exemplary pancreatic cells that may     | tunnel syndrome and Dupuytren's        |

| (e.g., renal failure, nephropathy<br>and/or other diseases and disorders as<br>described in the "Renal Disorders"<br>section below), diabetic neuropathy, | nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, innotence (e.g., due to | diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma,        | disease, atheroselerosis, microwascular disease, hypertension, stroke, and other diseases and disorders as described in the                                  | "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision             | impairment (e.g., diabetic retinopathy<br>and blindues), ulcers and impaired<br>wound healing, and infection (e.g.,<br>infectious diseases and disorders as<br>described in the "Infectious  | Discases' section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity                    | and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low                        | concentrations of cytosolic calcium<br>compared to much higher<br>extracellular calcium. Extracellular<br>factors can cause an influx of | calcium, leading to activation of<br>calcium responsive signaling<br>pathways and alterations in cell<br>functions. Exemplary assays that | may be used or rotation or measure calcium flux by polypoptides of the invention (including antibodies and agonists or antagonists of the invention) include | assays disclosed in: Satin LS, et al,<br>Endocrinology, 136(10);4589-601<br>(1995);Mogami H, et al.,<br>Endocrinology, 136(7);2960-6<br>(1995); Richardson SB, et al., | Biochem J, 288 (Pt 3):847-51<br>(1992); and, Meats, JE, et al., Cell<br>Calcium 1989 Nov-Dec;10(8):535-41<br>(1989), the contents of each of which<br>is herein incorporated by reference in | its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCCT <sup>n</sup> ) and/or may be routinely generated. Exemplary pancreatic | cells that may be used according to these assays include HITTI 5 Cells. HITTI 5 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with |
|                                                                                                                                                           |                                                                                                                                          |                                                                                                                                           |                                                                                                                                                              |                                                                                                                                                                        |                                                                                                                                                                                              |                                                                                                                                                                                                  |                                                                                                                                                                                   |
|                                                                                                                                                           |                                                                                                                                          |                                                                                                                                           |                                                                                                                                                              |                                                                                                                                                                        |                                                                                                                                                                                              |                                                                                                                                                                                                  |                                                                                                                                                                                   |
|                                                                                                                                                           |                                                                                                                                          |                                                                                                                                           |                                                                                                                                                              |                                                                                                                                                                        |                                                                                                                                                                                              |                                                                                                                                                                                                  |                                                                                                                                                                                   |

| indications are complications associated with rustlin resistance.                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| SV40. These cells express glueagon, assurasstain, and glueocordioad receptors. The cells secrete insulin, their is simulated by glueose and glueagon and suppressed by a somalostatin or glueocorticoids. ATTCs (Rels. Lord and Asharout. Blochem. J. 129: 547-551. USA 78: 433-434, 1981. USA 78: 433-434, 1981. | phosphorylation of Elk-1, and canasures the phosphorylation of Elk-1, and carterion of carterion of carterion of carterion of carterion of carterion of carterion and carterion and carterion and carterion and carterion and carterion and carterion and carterion and carterion and carterion and carterion and carterion of the analysis of the carterion of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis o |
|                                                                                                                                                                                                                                                                                                                   | Inhibition of adipocyte PRK signaling pathway.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                   | 695                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                   | HNHFR04                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                   | 591                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                                                                                                                                     | astlam, allety preferred includations include astlam, allety, hypersensitivity because, and inflammation Preferred indications include infections incitor (e.g. an infections disease as described below under "Infections Disease"), immunological diseaters, immunological diseaters, immunological diseaters, Disease's, immunological diseaters, of the proposition of the proposition of the proposition of the proposition of the proposition include and promotion include autoinmune diseases (e.g., as autoinmune diseases (e.g., as autoinmune diseases (e.g., as described below) and immunodediciencies (e.g., as described below) and described below).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| were differentiated to an adjoose-like state before being used in the seven. See Green et al., Cell 3: 1.27-133 (1974), the contents of which are herein incorporated by reference in its entirety. | transacription through the NFRB reasons cleaner are well-known in the rat and may be used or toutinely modified to assess the a hilly of polyperides of the invention or invention in the rat and may be used or toutinely modified to assess the a hilly of polyperides of the invention to regulate NFRB transacription factors and amonitate or the invention of regulate NFRB transacription factors in manipulated by the properior of the invention of the properior of the invention of the properior of the invention of the properior of the invention of the latter and a consequence of the invention of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latter of the latt |
|                                                                                                                                                                                                     | Transartijoon through<br>Transartijoon through<br>Alexan rayamas<br>Alexand in immane<br>calls (sach us EOL)<br>calls).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                                                                                                                                     | 165                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| reporter assay (which measures from the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of | firms easy, Kinen essay, for example an GSK-3 kines essay, for PIS kines essay, for PIS kines espay, for example an GSK-3 kines essay, for PIS kines espain ethors metabolism and cell survivial are well-known in the art and may be used or roalinely modified to assess the ability of polypeptides of the invention (including ambedies and agoniss or augusons or their invention) to promote or inhibit ghoose metabolism and cell survival.  Textuplary assays for PIS kines—diduced activity that may be used or routinely exception of the activity of polypeptides of the activity that may be used or routinely exception of the activity of polypeptides of the activity of polypeptides of the activity of polypeptides of the activity of polypeptides of the activity of polypeptides of the activity of polypeptides of the activity of polypeptides of the activity of polypeptides and activity of polypeptides and automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automists of their automist of automists of their automists of their automists of their automist of automists of their automists of their automists of their automists of their automists of their automistic part and activity of polyperides and automists of their automistic part automist of automistic part automistic part automistic part automist of automistic part automistic part automistic part automistic part automistic part automist part automist part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part automistic part a |
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| invention) include assays disclosed in       | preferred embodiment of the             |
|----------------------------------------------|-----------------------------------------|
| Forrer et al., Biol Chem 379(8-              | invention includes a method for         |
| 9):1101-1110 (1998); Nikoulina et            | stimulating muscle cell                 |
| al., Diabetes 49(2):263-271 (2000);          | differentiation. In a specific          |
| and Schreyer et al., Diabetes                | embodiment, skeletal muscle cell        |
| 48(8):1662-1666 (1999), the contents         | differentiation is stimulated. An       |
| of each of which are herein                  | alternative highly preferred            |
| incorporated by reference in its             | embodiment of the invention             |
| entirety. Rat myoblast cells that may        | includes a method for inhibiting        |
| be used according to these assays are        | muscle cell differentiation. In a       |
| publicly available (e.g., through the        | specific embodiment, skeletal muscle    |
| ATCC <sup>TM</sup> ). Exemplary rat myoblast | cell differentiation is inhibited.      |
| cells that may be used according to          | Highly preferred indications include    |
| these assays include L6 cells. L6 is         | disorders of the musculoskeletal        |
| an adherent rat myoblast cell line,          | system. Preferred indications           |
| isolated from primary cultures of rat        | include neoplastic diseases (e.g., as   |
| thigh muscle, that fuses to form             | described below under                   |
| multinucleated myotubes and striated         | "Hyperproliferative Disorders"),        |
| fibers after culture in differentiation      | endocrine disorders (e.g., as           |
| media.                                       | described below under "Endocrine        |
|                                              | Disorders"), neural disorders (e.g., as |
|                                              | described below under "Neural           |
|                                              | Activity and Neurological               |
|                                              | Diseases"), blood disorders (e.g., as   |
|                                              | described below under "Immune           |
|                                              | Activity", "Cardiovascular              |
|                                              | Disorders", and/or "Blood-Related       |
|                                              | Disorders"), immune disorders (e.g.,    |
|                                              | as described below under "Immune        |
|                                              | Activity"), and infection (e.g., as     |
|                                              | ģ                                       |
|                                              | Disease"). A highly preferred           |
|                                              | indication is diabetes mellitus.        |
|                                              | An additional highly preferred          |
|                                              | indication is a complication            |
|                                              | associated with diabetes (e.g.,         |
|                                              | diabetic retinopathy, diabetic          |

| nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disenders as described in the "Real Disorders" section belowy direktir, neuronathy | revre disease, in drawed manage (e.g., the to disease, the to disease, the temporally, blood vessel blookage, thent disease, starke, impotence (e.g., due to disease, the temporally or blood vessel blookage, sease, sease, mental bodiskap, sease, sease, mental ooutliston, drawsiness, another disease, and disease, sease, mental ooutliston, drawsiness, another disease, sease, and design, sease, and design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of the design of | hyperglycemic-hyperosmolar coma, cardiovascular disease, et g., heart disease, admonsferresis, minovivessular disease, hyperdension, stroke, and other diseases and diseases and other diseases and et "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (se described in the "Endocrine Disorders" section below). | helow), neuropathy vision impairment (e.g., diabetic retinopathy vision and blindness), ulcers and impaired wound healing, infections (e.g., infections (e.g., infections (e.g., infections diseases) sand disorders as described in the "Infections (e.g., infections diseases)" section below, especially Oriental Physics of the trimany react and skin), carpil tunned syndrome and Dipulyteral intended to the physics of the trimany reaction and indication is obesity and of complications associated with obesity. Additional highly preferred indications is obesity and overgrand in the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property o |
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|     |         |     |                       |                                       | Additional highly preferred           |
|-----|---------|-----|-----------------------|---------------------------------------|---------------------------------------|
|     |         |     |                       |                                       | indications are complications         |
|     |         |     |                       |                                       | associated with insulin resistance.   |
|     |         |     |                       |                                       | Additional highly preferred           |
|     |         |     |                       |                                       | indications are disorders of the      |
|     |         |     |                       |                                       | musculoskeletal system including      |
|     |         |     |                       |                                       | myopathies, muscular dystrophy,       |
|     |         |     |                       |                                       | and/or as described herein.           |
|     |         |     |                       |                                       | Additional highly preferred           |
|     |         |     |                       |                                       | indications include: myopathy,        |
|     |         |     |                       |                                       | atrophy, congestive heart failure,    |
|     |         |     |                       |                                       | cachexia, myxomas, fibromas,          |
|     |         |     |                       |                                       | congenital cardiovascular             |
|     |         |     |                       |                                       | abnormalities, heart disease, cardiac |
|     |         |     |                       |                                       | arrest, heart valve disease, and      |
|     |         |     |                       |                                       | vascular disease. Highly              |
|     |         |     |                       |                                       | preferred indications include         |
|     |         |     |                       |                                       | neoplasms and cancer, such as,        |
|     |         |     |                       |                                       | rhabdomyoma, rhabdosarcoma,           |
|     |         |     |                       |                                       | stomach, esophageal, prostate, and    |
|     |         |     |                       |                                       | urinary cancer. Preferred indications |
|     |         |     |                       |                                       | also include breast, lung, colon,     |
|     |         |     |                       |                                       | pancreatic, brain, and liver cancer.  |
|     |         |     |                       |                                       | Other preferred indications include   |
|     |         |     |                       |                                       | benign dysproliferative disorders and |
|     |         |     |                       |                                       | pre-neoplastic conditions, such as,   |
|     |         |     |                       |                                       | hyperplasia, metaplasia, and/or       |
|     |         |     |                       |                                       | dysplasia.                            |
|     | HNHFR04 | 695 | Activation of         | Assays for the activation of          | Preferred embodiments of the          |
| 165 |         |     | transcription through | transcription through the NFKB        | invention include using polypeptides  |
|     |         |     | NFKB response         | response element are well-known in    | of the invention (or antibodies,      |
|     |         |     | element in neuronal   | the art and may be used or routinely  | agonists, or antagonists thereof) in  |
|     |         |     | cells (such as SKNMC  | modified to assess the ability of     | detection, diagnosis, prevention,     |
|     |         |     | cells).               | polypeptides of the invention         | and/or treatment of Neurological      |
|     |         |     |                       | (including antibodies and agonists or | Diseases and Disorders (e.g.          |
|     |         |     |                       | antagonists of the invention) to      | Alzheimer"s Disease, Parkinson"s      |
|     |         |     |                       | regulate NFKB transcription factors   | Disease, Brain Cancer, Seizures).     |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | A highly preferred indication is diabetes mellins. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic reimopathy, diabetic nephropathy, kidney disease |
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| and modulate expression of neutronal ages. Exemplar seasons for transcription through the VRKB response element and may be used or nontimely modified to test VHKBs response element activity of poppersisties of the invention of hopopaphics and agoinsts or anatomisms of the invention included malobacies and agoinsts or anatomisms of the invention include anatomisms of the invention include anatomisms of the invention include anatomisms of the invention include anatomisms of the invention include Season (1998); Edward (1998); Callen and Mannami M. et al., 118 of Cacn. (6-110 (1998); Cullen and al., Gare (6-110 (1998); Cullen and Alman Methods in Enzymol 118 (1997); Heafmon et al., 1634–284 (1998); Heafmon et al., 1634, 1634 (1998); Walle Blacquez et al., 1634, 1634 (1998); Walle Blacquez et al., 1634, 1634 (1998); Walle Blacquez et al., 294); St. St. St. 164 (1999); Heafmon et al., 294); St. St. St. 164 (1999); The service of the content of clear of which are never in incorparated by reference in its incorparated by reference in its incorparated by reference in its incorparated by reference in its incorparated by reference in its incorparated by reference in its incorparated by reference in its incorparated by reference in the fall may be used according to these assays are publicly available (e.g., funglish to current). | Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Regulation of<br>transcription through<br>the PEPCK promoter in<br>hepatocytes                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 570                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HNHNB29                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 166                                                                                                                                                                                                      |

|     | (e.g., renai faiture, nephropatny     | and/or other diseases and disorders as | described in the "Kenal Disorders" | section below), diabetic neuropathy,  | nerve disease and nerve damage    | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to      | diabetic neuropathy or blood vessel  | blockage), seizures, mental         | confusion, drowsiness, nonketotic   | hyperglycemic-hyperosmolar coma, | _                                      | disease, atherosclerosis,           | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine      | disorders (as described in the         | "Endocrine Disorders" section    | below), neuropathy, vision       | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., an | infectious diseases or disorders as  | Ť                                 | _                                    | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's   | contracture). An additional           | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred |
|-----|---------------------------------------|----------------------------------------|------------------------------------|---------------------------------------|-----------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|----------------------------------|----------------------------------|----------------------------------------|-------------------------------------|------------------------------------|--------------------------------------|-----------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|
| 5 5 | (including antibodies and agonists or | antagomsts of the invention) to        | activate the PEPCK promoter in a   | reporter construct and regulate liver | gluconeogenesis. Exemplary assays | for regulation of transcription     | through the PEPCK promoter that       | may be used or routinely modified to | test for PEPCK promoter activity (in | hepatocytes) of polypeptides of the | invention (including antibodies and | agonists or antagonists of the   | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Culten and Malm, Methods in          | Enzymol 216:362-368 (1992);    | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988);           | Lochhead et al., Diabetes 49(6):896- | 903 (2000); and Yeagley et al., J Biol | Chem 275(23):17814-17820 (2000), | the contents of each of which is | herein incorporated by reference in    | its entirety. Hepatocyte cells that | may be used according to these     | assays are publicly available (e.g., | through the ATCCTM) and/or may be | routinely generated. Exemplary liver | hepatoma cells that may be used        | according to these assays include | H4lle cells, which contain a tyrosine | amino transferase that is inducible    | with glucocorticoids, insulin, or    | cAMP derivatives.                    |                                    |                             |                             |
| _   |                                       |                                        |                                    |                                       |                                   |                                     |                                       |                                      |                                      |                                     |                                     |                                  |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |
|     |                                       |                                        |                                    |                                       |                                   |                                     |                                       |                                      |                                      |                                     |                                     |                                  |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             | _                           |

|  | indications are complications           |
|--|-----------------------------------------|
|  | mercanons are compromise                |
|  | associated with insulin resistance.     |
|  | Additional highly preferred             |
|  | indications are disorders of the        |
|  | musculoskeletal systems including       |
|  | myopathies, muscular dystrophy,         |
|  | and/or as described herein.             |
|  | Additional highly preferred             |
|  | indications include glycogen storage    |
|  | disease (e.g., glycogenoses),           |
|  | hepatitis, gallstones, cirrhosis of the |
|  | liver, degenerative or necrotic liver   |
|  | disease, alcoholic liver diseases,      |
|  | fibrosis, liver regeneration, metabolic |
|  | disease, dyslipidemia and cholesterol   |
|  | metabolism, and hepatocarcinomas.       |
|  | Highly preferred indications include    |
|  | blood disorders (e.g., as described     |
|  | below under "Immune Activity",          |
|  | "Cardiovascular Disorders", and/or      |
|  | "Blood-Related Disorders"), immune      |
|  | disorders (e.g., as described below     |
|  | under "Immune Activity"), infection     |
|  | (e.g., an infectious disease and/or     |
|  | disorder as described below under       |
|  | "Infectious Disease"), endocrine        |
|  | disorders (e.g., as described below     |
|  | under "Endocrine Disorders"), and       |
|  | neural disorders (e.g., as described    |
|  | below under "Neural Activity and        |
|  | Neurological Diseases").                |
|  | Additional preferred indications        |
|  | include neoplastic diseases (e.g., as   |
|  | described below under                   |
|  | "Hyperproliferative Disorders").        |
|  | Preferred indications include           |
|  | neoplasms and cancers, such as,         |

|     |         |     |                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | the detail, hypholom, prostate, breast, lung, colon, pancretatic, colon, pancretatic, colon, pancretatic, colon, pancretatic, and urinary cancer. A highly preferred urinary cancer. A highly preferred readent is a cancer. Other preferred indication is there are accept the preferred indications include benign preferred indications include benign monoplastic conditions such as, for conditions such as, for cancer, by, type-cplustin, metaplastin, metaplastin, and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and present and |
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| 167 | HNHOD46 | 571 | Activation of Activation of Adprovate BRK Signaling Palitway | Kitmes easy, Kitmes easys, for example an III-1 kinne assay, for IRA signal translution that regular earth of the proliferation of differentiation are well pollogenous of differentiation are well pollogenous of differentiation and eases the shilty of polypeptides of the invention (including antibodies and agonists or amagonists of the or amagonists of the proliferation, activation, and promote or inhibit cell proliferation, activation, and which are the same agonists of the invention of profile and activity that may be used to containely medified to test ERK kinness eartherly of polyperbids of the invention) include kinness-inthord activity of polyperbids of the invention) include antibodies and agoniss of the invention) include antibodies and agonis of the invention include antibodies and agonis of the invention include. Biodic Chem 379(&-5); 1101-1100 Clin Endocrinol Diabetes and activated and Karth Nature 44 (1999); Kyristakis JM, Biochem Soc Symp 64.29-48 (1999). | A highly preferred embodiment of the investion includes a method for simmalating adhocyte prodiferation. An alternative highly preferred embodiment of the mirroration includes a method for inchestion and produced embodiment of the inchestion and produced embodiment of the inchestion and produced embodiment of the inchestion and produced embodiment of the inchestion and produced embodiment of the inchestion and the produced embodiment of the investion includes a method for inchitation adjaces a method for inchitation and particular and alternative inchitation for activation (c.g., increasing) adjaces activation. An alternative inchitation for activation (c.g., decreasing) and or inservitorium adjacestics. Illegibly preferred inchitation for activation (c.g., decreasing) and or inservitorium adjacestics a laginy preferred including and allegibly preferred including and allegibly preferred indications include embodrate adjacestics. Inflighty preferred including and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegible and allegibl |
|     |         |     |                                                              | (1998); Le Marchand-Brustel Y, Exp<br>Clin Fathodroinol Dispeteres<br>(107(2):126-132 (1999); Kyrakisi M,<br>Biochem Soe Symp 64:29-48 (1999);<br>Chag and Karin, Nature<br>41(06824)37-40 (2001); and Cobb<br>MH, Prog Biophys Mol Biol 71(3-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | inhibiting the activation of (e.g., decreasing) and or inactivating adipocytes. Highly preferred indications include endocrine indications include endocrine of a described below that the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the |

| cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly | preferred indications are | complications associated with insulin | resistance. Additional highly | preferred indications are disorders of | the musculoskeletal systems | including myopathies, muscular | dystrophy, and/or as described | herein. Additional highly | preferred indications include, | hypertension, coronary artery | disease, dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, | eating disorders, fibrosis, cachexia, |
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|                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |                                      |                                      |                         |                           |                                       |                               |                                        |                             |                                |                                |                           |                                |                               |                                    |                                         |                                       |
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| Pregrand indications include neopleans and ease, such as humbown, teleternia and breast, cook, and stimmt such as the cook, and stimmt, and the cook and stimmt, they are more allowing partnered, esophaged, stormer, infigibly preferred indications include information and preservenae. Other preferred indications include in preferred indications include being prepared indications include being preferred indications include being preferred indications include being preferred indications include being prepared indications include being prepared indications include being caracter and pre- | F A highly preferred indication is a chiefure a real indications included with chiefure and preferred indications included with chiefure and produced with chiefure and produced with chiefure proposality, kintery disabetes (e.g., renal failure, nephropathy and disabetes and disabete in the "Renal Disorders" (such andro other diseases and disabete and other disease and nerve disasses and disabete and constitution, to make a constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do constitution, do const |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Assays for the regulation of transacription through the DMFF response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention) to activate the DMFF i response element in a support construct (such as that containing the GLUT4 about the DMFF i response element in a proport construct (such as that containing the GLUT4 to activate the DMFF i response element is present in the GLUT4 transcription factor and another transacription factor and another transcription factor and another for insulin regulation of Glut4 for insulin regulation of Glut4 for insulin regulation of Glut4 for insulin regulation of Glut4 for insulin regulation of Glut4 and remostly is the primary insulin- GLUT4 is the primary insulin- call transcription factor and another transcription factor and another for insulin- GLUT4 is the primary insulin- call transcription factor and another transport in factor and another transport in the contrast its present in the contrast its many primary insulin- call transcription factor and another transport in factor and another transport in the contrast its present in the contrast its required for insulin- call transcription factor and another transport in the contrast its present in the contrast its required for insulin- call transcription factor and another transport in the contrast its required for insulin-  CLUT4 is the primary insulin-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | transcription via<br>programme and programme administration of<br>and pre-adipocytes<br>and pre-adipocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 571                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HNHOD44                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                          | A highly preferred indication is | obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. An additional highly preferred | indication is diabetes mellitus. An   | additional highly preferred indication | is a complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy   | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage      | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to       | diabetic neuropathy or blood vessel | blockage), seizures, mental        | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section        | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired |
|----------------------------------------------------------|----------------------------------|------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|----------------------------------------|------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|--------------------------------------|----------------------------|----------------------------------------|-------------------------------------|
| under appropriate differentiation<br>culture conditions. |                                  |                              | response element are well-known in  | the art and may be used or routinely | modified to assess the ability of    | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) to       |                                   | ate                                   | expression of genes involved in a    | wide variety of cell functions. For | example, a 3T3-L1/CRE reporter         | ors                                | that activate the cAMP signaling     | pathway. CREB plays a major role in | adipogenesis, and is involved in    | differentiation into adipocytes. CRE  | contains the binding sequence for the |                                     | binding protein). Exemplary assays | for transcription through the cAMP | d or                             | MP-                                 |                           | polypeptides of the invention        |                                | nde                           | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol       | 216:362-368 (1992); Henthorn et al., | _                          | 퓻                                      | Biol 20(3):1008-1020 (2000); and    |
|                                                          | Activation of                    | transcription through        | cAMP response                       | element (CRE) in pre-                | adipocytes.                          |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                    |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                                      |                            |                                        |                                     |
|                                                          | 571                              |                              |                                     |                                      |                                      |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                    |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                                      |                            |                                        |                                     |
|                                                          | HNHOD46                          |                              |                                     |                                      |                                      |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                    |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                                      |                            |                                        |                                     |
|                                                          |                                  | 167                          |                                     |                                      |                                      |                                      |                                       |                                        |                                   |                                       |                                      |                                     |                                        |                                    |                                      |                                     |                                     |                                       |                                       |                                     |                                    |                                    |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                                      |                            |                                        |                                     |

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| 167 | HNHOD46 | 571 | Activation of<br>transartipon through<br>serum response clement<br>in pre-adipocytes. | transcription through the Sexum transcription through the Sexum the Sexum Element (SER) are well- known in the art and may be used or noutinely modified to usesse the ability of pohypepitelses and against a magnonists of the invention (including antibodies and against or anagonists of the invention) to regulate the serum transcription of genes involved in expression of genes involved in expression of genes involved in transcription through the SER that                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | he highly proferred indication is obesity and/or complications obesity and/or complications assistantly and/or complications of the professional with object of the professional control indications include weight loss or distructively, weight with a validational highly preferred indication is disheres mellitars. An additional highly preferred indication is a complication associated with disheres (e.g., dishere is e.g. and mitture, the photophity, idding disease, and dishere unphropathy disease and on the phropography disease and control in the phropography disease. |
|     |         |     |                                                                                       | may be used or routinely modified to<br>test SRE activity of the polypeptides<br>of the invention (including antibodies<br>and agonists or antagonists of the<br>invention) include assays disclosed in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | described in the "Renal Disorders"<br>section below), diabetic neuropathy,<br>nerve disease and nerve dennage<br>(e.g., due to diabetic neuropathy),<br>blood vessel blockage, heart disease,                                                                                                                                                                                                                                                                                                                                                                                              |

| Pargent et al., Grone 66:1-10(1998). Cultin and Malin, Methods in Enzyman Di (252-256(1992); Herulmont et al., Proc Natl Acad 52(1902); Herulmont et al., Proc Natl Acad 52(1902); Sel Se 56-564(1988); Black et al., Virus Genes 12(2):10(2); As 56-56-546(1988); Black et al., Virus Genes 12(2):10(2); Proc content of each of which are becrein incorporated by reference, in les tuntoy; Proc adaptocycle tunto by the ATCUN and adaptocycle tunto by the ATCUN and adaptocycle tunto by the ATCUN and adaptocycle tunto by the ATCUN and adaptocycle tunto by the ATCUN and adaptocycle tunto by the ATCUN and adaptocycle tunto by the acad according to these sassys include 1371-L (cell, 377-L); an addrectul mouse preclaphocycle as conditions substrain of 373 firm-bals cells calculated as to adaptocycle to adiposible conversation under appropriate of inferentiation conditions known in the art.  Assays for the atvantion of Assays for the art and may be used a custom as well-shown in the art and may be used or routinely increase challe and agencies of the invention increase challe and expression of genes involved in a maganist of the invention in creases challenger are well-shown in the art and may be used or routinely increase challenger and may be used or routinely increase challenger and may be used or routinely increase challenger are well-shown in the art and may be used or routinely increase challenger and may be used or routinely increase challenger are remargentiates of the invention in creases the ability of polypoptics of the invention in creases the admitty of polypoptics of the invention in creases the admitty of a polypoptic and are all and the art and may be used or routinely increases the admitty of a polypoptics of the invention in creases the admitty of a polypoptics of the invention in creases the admitty of a polypoptics of the invention in creases the admitty of a polypoptic and an admitted and an admitted and an admitted and an admitted and an admitted and an admitted and an admitted and an admitted and an admitte |
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| described below), boosting a T cell- | suppressing a T cell-mediated  | immune response. Additional         | preferred indications include       | nflammation and inflammatory       | lers. Highly preferred                 | indications include neoplastic      | diseases (e.g., leukemia, lymphoma, | and/or as described below under | 'Hyperproliferative Disorders").    | Highly preferred indications include | neoplasms and cancers, such as, for | example, leukemia, lymphoma (e.g., | T cell lymphoma, Burkitt's         | ymphoma, non-Hodgkins                | ymphoma, Hodgkin"s disease),     | nelanoma, and prostate, breast, lung, | colon, pancreatic, esophageal,         | stomach, brain, liver and urinary | cancer. Other preferred indications           | include benign dysproliferative     | disorders and pre-neoplastic       | conditions, such as, for example,     | nyperplasia, metaplasia, and/or | lysplasia. Preferred indications | nclude anemia, pancytopenia, | eukopenia, thrombocytopenia, acute | ymphocytic anemia (ALL), | plasmacytomas, multiple myeloma, | arthritis, AIDS, granulomatous | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, | psoriasis, suppression of immune | eactions to transplanted organs and | tissues, hemophilia, |
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| $\vdash$                             | - 0,                           |                                     | _                                   |                                    | ŭ                                      |                                     | _                                   | -                               | •                                   | -                                    |                                     | -                                  | _                                  | _                                    | _                                | _                                     | re publicly                            |                                   | se T cells                                    | -<br>-                              | _                                  | ÷                                     | _                               | dyspl                            | includ                       | leukoj                             | lymbl                    | plasm                            | arthrit                        | diseas                               | sebsis                             | psoria                           | reacti                              | tissne               |
| through the cAMP response element    | modified to test cAMP-response | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in         | Enzymol 216:362-368 (1992);     | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Black et    | al., Virus Genes 15(2):105-117      | (1997); and Belkowski et al., J    | Immunol 161(2):659-665 (1998), the | contents of each of which are herein | incorporated by reference in its | entirety. T cells that may be used    | according to these assays are publicly | available (e.g., through the      | ATCC <sup>TM</sup> ). Exemplary mouse T cells | that may be used according to these | assays include the CTLL cell line, | which is a suspension culture of IL-2 | dependent cytotoxic T cells.    |                                  |                              |                                    |                          |                                  |                                |                                      |                                    |                                  |                                     |                      |
|                                      |                                |                                     |                                     |                                    |                                        |                                     |                                     |                                 |                                     |                                      |                                     |                                    |                                    |                                      |                                  |                                       |                                        |                                   |                                               |                                     |                                    |                                       |                                 |                                  |                              |                                    |                          |                                  |                                |                                      |                                    |                                  |                                     |                      |
|                                      |                                |                                     |                                     |                                    |                                        |                                     |                                     |                                 |                                     |                                      |                                     |                                    |                                    |                                      |                                  |                                       |                                        |                                   |                                               |                                     |                                    |                                       |                                 |                                  |                              |                                    |                          |                                  |                                |                                      |                                    |                                  |                                     |                      |
|                                      |                                |                                     |                                     |                                    |                                        |                                     |                                     |                                 |                                     |                                      |                                     |                                    |                                    |                                      |                                  |                                       |                                        |                                   |                                               |                                     |                                    |                                       |                                 |                                  |                              |                                    |                          |                                  |                                |                                      |                                    |                                  |                                     |                      |
|                                      |                                |                                     |                                     |                                    |                                        |                                     |                                     |                                 |                                     |                                      |                                     |                                    |                                    |                                      |                                  |                                       |                                        |                                   |                                               |                                     |                                    |                                       |                                 |                                  |                              |                                    |                          |                                  |                                |                                      |                                    |                                  |                                     |                      |

| endocarditis, meningitis, Lyme<br>Disease, and asthma and allergy. | invention includes a method for invention includes a method for invention includes a method for including (e.g., reducing). The alpha production, An alternative preferred methodrient of the invention includes a method for simulating (e.g., reducing). The alpha production, and includes a method for simulating production. The farm and the blood disable for e.g. as a described below under "Immune Preferred indications reduces", and for "Cardiovaecular Disanders", Halphy preferred Disanders", Halphy preferred indications include autoimment of the productions include autoimment of the productions include autoimment of the producing include autoimment of the producing and activities of the producing and a described below), immuned related immune response, and an excepted below, bossing a T cell-mediated immune response, and antimization is included minimum or supposes, and antimization is included minimum engoines. Highly preferred inflammation and inflammation and inflammation and inflammation and inflammation included morphastic diseases (e.g., leucenia, in patients with relearned inflammation and inflammation included morphastic diseases (e.g., leucenia, helpow, under "Hyperemolificative").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Disorders"). Additionally, highly<br>preferred indications include |
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|                                                                    | transcription through the Searum<br>Seasons for the advantage of the season the<br>transcription through the Searum<br>Seasons Element (SRS) are well-<br>seasons for the season to<br>abund the season to<br>the season of the season to<br>the season of the season to<br>against or pulypeptides of the<br>against or anagomists of the<br>against or anagomists of the<br>against or anagomists of the<br>seasons of genes involved in<br>responses factors and modilate the<br>seasons of genes involved in<br>personne factors and modilate the<br>seasons of genes involved in<br>growth. Exemplary assays for<br>proposed to<br>may be used or rounteely modified to<br>and agonists or anagomists of the<br>and agonists or anagomists of the<br>and agonists or anagomists of the<br>modified and March Methods in<br>Element al. Prov Ball Acad<br>Sci 562-563 (1992), in<br>Element al. Prov Ball Acad<br>Sci 562-563 (1992), in the content of each of<br>the content of each o | ь                                                                  |
|                                                                    | Advantage of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the cont                                                                                                                                                     |                                                                    |
|                                                                    | 1/6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                    |
|                                                                    | INHOW PARTY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                    |
|                                                                    | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                    |

|     |         |     |                    |                                      | neoplasms and cancers, such as, for   |
|-----|---------|-----|--------------------|--------------------------------------|---------------------------------------|
|     |         |     |                    |                                      | example, leukemia, lymphoma,          |
|     |         |     |                    |                                      | melanoma, glioma (e.g., malignant     |
|     |         |     |                    |                                      | glioma), solid tumors, and prostate,  |
|     |         |     |                    |                                      | breast, lung, colon, pancreatic,      |
|     |         |     |                    |                                      | esophageal, stomach, brain, liver and |
|     |         |     |                    |                                      | urinary cancer. Other preferred       |
|     |         |     |                    |                                      | indications include benign            |
|     |         |     |                    |                                      | dysproliferative disorders and pre-   |
|     |         |     |                    |                                      | neoplastic conditions, such as, for   |
|     |         |     |                    |                                      | example, hyperplasia, metaplasia,     |
|     |         |     |                    |                                      | and/or dysplasia. Preferred           |
|     |         |     |                    |                                      | indications include anemia,           |
|     |         |     |                    |                                      | pancytopenia, leukopenia,             |
|     |         |     |                    |                                      | thrombocytopenia, Hodgkin's           |
|     |         |     |                    |                                      | disease, acute lymphocytic anemia     |
|     |         |     |                    |                                      | (ALL), plasmacytomas, multiple        |
|     |         |     |                    |                                      | myeloma, Burkitt's lymphoma,          |
|     |         |     |                    |                                      | arthritis, AIDS, granulomatous        |
|     |         |     |                    |                                      | disease, inflammatory bowel disease,  |
|     |         |     |                    |                                      | neutropenia, neutrophilia, psoriasis, |
|     |         |     |                    |                                      | suppression of immune reactions to    |
|     |         |     |                    |                                      | transplanted organs and tissues,      |
|     |         |     |                    |                                      | hemophilia, hypercoagulation,         |
|     |         |     |                    |                                      | diabetes mellitus, endocarditis,      |
|     |         |     |                    |                                      | meningitis, Lyme Disease, cardiac     |
|     |         |     |                    |                                      | reperfusion injury, and asthma and    |
|     |         |     |                    |                                      | allergy. An additional preferred      |
|     |         |     |                    |                                      | indication is infection (e.g., an     |
|     |         |     |                    |                                      | infectious disease as described below |
|     |         |     |                    |                                      | under "Infectious Disease").          |
|     | HNHOD46 | 571 | Production of IL-6 | IL-6 FMAT. IL-6 is produced by T     | A highly preferred embodiment of      |
| 167 |         |     |                    | cells and has strong effects on B    | the invention includes a method for   |
|     |         |     |                    | cells. IL-6 participates in IL-4     | stimulating (e.g., increasing) IL-6   |
|     |         |     |                    | induced IgE production and increases | production. An alternative highly     |
|     |         |     |                    | IgA production (IgA plays a role in  | preferred embodiment of the           |
|     |         |     |                    | mucosal immunity). IL-6 induces      | invention includes a method for       |

| cutotoxic T cells Denomiated           | A. II (painther a a) mithidiai         |
|----------------------------------------|----------------------------------------|
| expression of II -6 has been linked to | production A highly preferred          |
| autoimmune discase, plasmacytomas,     | indication is the stimulation or       |
| myelomas, and chronic                  | enhancement of mucosal immunity.       |
| hyperproliferative diseases. Assays    | Highly preferred indications include   |
| for immunomodulatory and               | blood disorders (e.g., as described    |
| differentiation factor proteins        | below under "Immune Activity",         |
| produced by a large variety of cells   | "Blood-Related Disorders", and/or      |
| where the expression level is strongly | "Cardiovascular Disorders"), and       |
| regulated by cytokines, growth         | infection (e.g., as described below    |
| factors, and hormones are well         | under "Infectious Disease"). Highly    |
| known in the art and may be used or    | preferred indications include          |
| routinely modified to assess the       | autoimmune diseases (e.g.,             |
| ability of polypeptides of the         | rheumatoid arthritis, systemic lupus   |
| invention (including antibodies and    | erythematosis, multiple sclerosis      |
| agonists or antagonists of the         | and/or as described below) and         |
| invention) to mediate                  | immunodeficiencies (e.g., as           |
| immunomodulation and                   | described below). Highly preferred     |
| differentiation and modulate T cell    | indications also include boosting a B  |
| proliferation and function.            | cell-mediated immune response and      |
| Exemplary assays that test for         | alternatively suppressing a B cell-    |
| immunomodulatory proteins evaluate     | mediated immune response. Highly       |
| the production of cytokines, such as   | preferred indications include          |
| IL-6, and the stimulation and          | inflammation and inflammatory          |
| upregulation of T cell proliferation   | disorders. Additional highly preferred |
| and functional activities. Such        | indications include asthma and         |
| assays that may be used or routinely   | allergy. Highly preferred indications  |
| modified to test immunomodulatory      | include neoplastic diseases (e.g.,     |
| and diffferentiation activity of       | myeloma, plasmacytoma, leukemia,       |
| polypeptides of the invention          | lymphoma, melanoma, and/or as          |
| (including antibodies and agonists or  | described below under                  |
| antagonists of the invention) include  | "Hyperproliferative Disorders").       |
| assays disclosed in Miraglia et al., J | Highly preferred indications include   |
| Biomolecular Screening 4:193-          | neoplasms and cancers, such as,        |
| 204(1999); Rowland et al.,             | myeloma, plasmacytoma, leukemia,       |
| "Lymphocytes: a practical approach"    | lymphoma, melanoma, and prostate,      |
| Chapter 6:138-160 (2000); and          | breast, lung, colon, pancreatic,       |
|                                        |                                        |

|     |         |     |                             | Verhasselt et al., I Immunol circusses of each of which are been of each of which are been of each of which are been entirely. Human dendritic cells that entirely. Human dendritic cells that may be used according to these assays may be isolated using using the entirely. Human dendritic or of the entirely estimated side edged been or otherwise known in the art. Human dendritic cells are antigen presenting except in supersions culture, which, when activated by antigen and/or exclusive standard and underly destinated and unde | esoplageal, stomach, brain, liver and mindro cancer (Other preferred indications include being in micro cancer (Other preferred indications include being in coopilisative cloudification and pre- neoplastic conditions, such as, for example, hypophilasin, metaplasin, and ord sysplasin, Preferred in microtical profiles and ord sysplasin, Preferred in microtical profilesian, preferred in microtical profilesian, preferred in microtical profilesian, preferred in practical proposition, ledskopenia, themmosyspornia, ledskopenia, themmosyspornia, ledskopenia, forth, multiple enycloma, Burktet's granthormator disease, neurophilia, AIDS, granthormator disease, profilesia, neurophilia, posticiasis, suppression or demogration of states, hemophilia, and copiens and itsues, hemophilia, and Lyme endocardiis meningiis, nd Lyme endocardiis meningiis, and Lyme endocardiis meningiis, and Lyme endocardiis meningiis, and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lyme endocardiis meningiis and Lym |
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|     |         |     |                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | indication is infection (e.g., an<br>infectious disease as described below<br>under "Infectious Disease").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 167 | HNHOD46 | 571 | Production of<br>MIP talpha | MIP-1alpha FMAT. Assays for immunonoidlatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotoxis are well known in the art and may be used or routinely.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | A highly preferred embodiment<br>of the invention includes a method<br>for stimulating MIP a production.<br>An alternative lightly preferred<br>embodiment of the invention<br>includes a method for inhibiting (e.g.,<br>reducine) MIP a moduction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|     |         |     |                             | modified to assess the ability of polypophodes of the invention (including antibodies and agonists or antagonists of the invention) to mediac immunomediation, modification modification modified themotoxis, and modulate chemotoxis, and modulate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | highly preferred indication is<br>infection (e.g. an infections disease<br>as described below under "Infectious<br>Disease"). Preferred indications<br>include blood disorders (e.g., as<br>described below under "Inmune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Activity", "Blood-Related<br>Disorders", and/or "Cartiovascular<br>Disorders"), Highly preferred<br>indications include autoimmune<br>indisease (e.g., theumatoid arthritis,<br>systemic lunss evthematois.                           |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | below under "Hyperpolificative Disorders"). Highly preferred indications include neoplasms and cancers, such as, lenkemin, lymphoma, prostate, breast, lung, colon, pancrettic, esophageat, stomach, brain, liver, and urinary                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| T cell differentiation. Exemplary assays that test for immunomedulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein as macrophage in flammatory protein labba (MIP-1a) and the activation | of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and invention (including antibodies and | aquoniss or attaquaiss of the investment on pinetals and the Miraglia et al., J Biomolecular Screening 4:193-204(1999); Sreaning 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approad" Chapter 6:138-160 (2009); Suttaporn and Eremin, J R Coll Sung Ednb 45(1)-9-19 (2001). | Abackes et al., Transpl Immunol 8(1):17-29 (2000), Verhasselt et al. J. Immunol 18:29/2020 (2000), Verhasselt et al. J. Lenkoe Boyly, and Nardelli et al. J. Lenkoe Bosh (6:82); (1999), the contents of each of which are herein incorporated by reference in its entirety. Human reference in its entirety. Human electrone in its entirety. Human electrone in sentirety. Human electrone in sentirety. Human electrone in sentirety. Human electrone in sentirety. Ruman electrone in sentirety. | isolated using techniques disclosed herein or otherwise known in the art. Human dendriic cells are antigen presenting cells in suspension culture, which, when activated antigen and/or cytokines, infinite and upregulate T cell proliferation and |
|                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                     |

| include benign dysproliferative<br>disorders and pre-neoplastic<br>conditions, such as, for example,<br>hyperplasia, metaplasia, and/or<br>dysplasia. | lightly preferred indications include allegy, softma, and rhinitis.  Additional preferred indications include allegy, softma, and rhinitis.  Additional preferred indications also disease as described below under "Internation and inflammatory diseases is described below under "Internation and inflammatory diseases is described below under "Internation and inflammatory diseases below the properties also include blood disorders (e.g., as described below under "Internation Englands"). Preferred indications also include blood disorders (e.g., as described below) under "Internation distances (e.g., as described below) and immunoderification (e.g., as and/or as described below) and immunoderification to gestribed below) and immunoderification to a described below on the allowed to preferred indications include neoplastic freast, lung, and on parcentic, explained, in the combination of the preferred below under "Hyperprolificative include benium consopiation conditions, such as for excepting in the preferred indications include benium consopiation conditions, such as for excepting in preferred indications include benium and pre-                                                             |
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| include be<br>disorders a<br>conditions<br>hyperplasi<br>dysplasia.                                                                                   | Highly p allergy, a allergy, a allergy, a allergy, a deligence of "Infection inflamment disorders inflamment disorders inflamment disorders include a described blooders. Disorders include a cheumato execution disorders include a cheumato execution disorders and/or as and/or as and/or as and/or as and/or as stomach, indication meleanom colon, pa stomach, increasing dysprotific disporders indication dysprotific disorders.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                       | This reporter assay measures activated in the GATA-3 signaling pathway in HMC-1 human mast cell in activation of the GATA-3 in mass cells has been infect to cytokine and membrane protein the activation of transcription. The activation of transcription the activation of transcription the activation of transcription of transcription of transcription of transcription of transcription of transcription for the invention to the invention of the invention of the invention of the invention of the invention of the part of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention floors regulate GATA-3 transcription floors and modulate expression of rans cell gents important for immune response development. Evernplany assays for exponse element activity of the invention included mathod the GATA-3 transcription flooring antibodies and agoniss or automation to the invention include assays disclosed in Berger et al., Cale Cas-13 (1982); Lidlen and Malm, Methods in Enzymen of the invention include assays disclosed in Berger et al., Proc Natl Acad Sci 1858, Sci 5642-161. |
|                                                                                                                                                       | Adviration of Adviration of CARTA-5 regions of CARTA-5 regions of CARTA-5 regions of care in immune cells (such as must cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                       | 271                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                       | нинор46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                       | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| indications include anemia, any openia, leukenia, throubocyopenia, leukenia, thrombocyopenia, leukenia, thrombocyopenia, leukenia, leuke | allegy, settlemel indications include allegy, ashum, and rhintiis, additional prefered indications include distincts and include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include inclu |
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| 64:563-571 (1999); Rodriguez- Barneo et al., Lud Immuno  20(1):3914-3924 (1999); Zheng and  29(1):3914-3924 (1999); Zheng and  29(1):3914-3924 (1999); Lang and Hendesson et al., Mol Cell Biol  (1962/3864-394 (1994), the contents  of cach or vinkin are bretin  of cach or vinkin are bretin  of cach or vinkin are bretin  centrey. Mast cells that may be used  controller. Showing the  ATCC*** Sexuplary human mast  centrey. Mast cells that may be used  avoiding to these assays are publicly  avoidable (e.g., through the  ATCC***). Sexuplary human mast  cells that may be used according to  these assays include the HMC-I cell  thin withel is an immature human  mast cell line established from the  preprincable hole of a patient with  mast cell luckernia, and exhibits  mast cell luckernia, and exhibits  many characteristics of immature  mast cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | activation of the NFAT signaling pathways in Research and activation of the NFAT signaling plants in the NFAT signaling plants in the NFAT signaling plants in the Activation of NFAT in mast cells has been linked to cytokine and the mention production. Assays for the activation of transcription the activation of transcription framewing the New Jacobs and Parket and Tool 8 (PFAT) response former are well-flowown in the art and may be used or routinely polypeptides of the invention of chieffiding analysis and all miscentification in an authorisis and agonists of the invention) to autagonists of the invention) to autagonists of the invention) to autagonists of the invention) to greats and modifiale expression of genes and modifiale expression of genes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Activation of transcription through NFAT response cleaners in immune cells (each as must cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|------------------------------|-------------------------------|--------------------------------|--------------------------------------|-----------------------------------|------------------------------|------------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|------------------------------------|-------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|--------------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------|-------------|---------------------------------|
| immunicate for a constraint  | decoulted telember Profession | indications include neonlastic | diseases (e.g. lenkemia lymphoma     | melanoma, prostate, breast, lung. | colon pancreatic esophageal  | stomach, brain, liver, and urinary | tract cancers and/or as described     | below under "Hyperproliferative       | Disorders"). Other preferred       | indications include benign      | dysproliferative disorders and pre- | neoplastic conditions, such as, for  | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred        | indications include anemia,        | pancytopenia, leukopenia,     | thrombocytopenia, leukemias, | Hodgkin's disease, acute         | lymphocytic anemia (ALL),        | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, sepsis, neutropenia, | neutrophilia, psoriasis, suppression  | of immune reactions to transplanted    | organs and tissues, hemophilia, | hypercoagulation, diabetes mellitus,       | endocarditis, meningitis, and Lyme  | Disease.                            |                                  |                                     |                                    |                                  |                                  |             |                                 |
| involved in immunoamodulotom | finotions Enougher coorse for | transcription through the NFAT | response element that may be used or | routinely modified to test NFAT-  | response element activity of | polyneptides of the invention      | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol            | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-   | 6346 (1988); De Boer et al., Int J | Biochem Cell Biol 31(10):1221-1236 | (1999); Ali et al., J Immunol | 165(12):7215-7223 (2000);    | Hutchinson and McCloskey, J Biol | Chem 270(27):16333-16338 (1995), | and Turner et al., J Exp Med     | 188:527-537 (1998), the contents of  | each of which are herein            | incorporated by reference in its    | entirety. Mast cells that may be used | according to these assays are publicly | available (e.g., through the    | ATCC <sup>TM</sup> ). Exemplary human mast | cells that may be used according to | these assays include the HMC-1 cell | line, which is an immature human | mast cell line established from the | peripheral blood of a patient with | mast cell leukemia, and exhibits | many characteristics of immature | mast cells. | Assays for the regulation (i.e. |
|                              |                               |                                |                                      |                                   |                              |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |                                  |                                      |                                     |                                     |                                       |                                        |                                 |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             | Proliferation of pre-           |
|                              |                               |                                |                                      |                                   |                              |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |                                  |                                      |                                     |                                     |                                       |                                        |                                 |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             | 571                             |
|                              |                               |                                |                                      |                                   |                              |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |                                  |                                      |                                     |                                     |                                       |                                        |                                 |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             | HNHOD46                         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Preferred indications include blood disorders (e.g. sed escribed below under"-Timmune Activity", "Blood-under"-Timmune Activity", "Blood-under"-Timmune Activity", and or "Cardiovascular Disorders", and infection (e.g. an infection (e.g. an infection (e.g. an infection (e.g. an infection (e.g. an infection (e.g. an infection (e.g. an infection infection) and infection infections infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infection infec |
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| and proliferation of cells in vitro as well-known in the ert and may be weel known in the ert and may be weel known in the ert and may be well-known in the ert and may be well-known in the ert and may be well-known in the ability of pohypeptides of the against of pohypeptides of the against of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the pohyperity of the p | Assays for the activation of reasons for transacription through the cAMP response element are well-known in the art and may be need or nouties) modified to assays the ability of hoppsprides of the invention (including antihodies and agonists or increase CAMP, blad to CREB invention) to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| adipose cells (such as 3T5-L1 cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Activation of<br>transcription through<br>cAMP response<br>element in immune<br>cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| psoriasis, suppression of immune<br>reactions to transpirated organs and<br>tissues, hemophilia,<br>hyperoagulation, diabetes mellitus,<br>endocarditis, meningitis, Lyme<br>Disease, and asthma and allergy. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                                                                                                                                                                                               | Advision from the Assays for the activation of Advision through the Nuclear MAT Trescaption through the Nuclear MAT Trescapts in Factor of Advision through the Nuclear MAT Trescapts in the art and may be used or routinely notified to assess the tability of polypoptides of the invention (including authorities and the invention) to amagainst of the invention) to amagainst of the invention) to amagainst of the invention of antiqual materials of the invention) to amagainst of the invention) to amagainst of the invention) to amagainst of the invention of including authorities and the invention of including authorities when the invention includes assays for the invention of including authorities and genisis or antiquely to active for the invention of including authorities and agonisis or antiquely and the invention in include assays disclosed in Berger et al.  Proc Math. Adento & Biochina and genisis or antiquent of the invention of including authorities and agonisis or antiquent of the invention of including authorities and agonisis or antiquent of the invention of including authorities and agonisis or antiquent of the invention of including authorities and agonisis or antiquent of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of  |
|                                                                                                                                                                                                               | Activation of Immessiphion Immessiphion NPAT responsiments of Incells.  T-cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|     |         |     |                       | 14303 (1003) the contents of each of    | include benien dreamelifemetics         |
|     |         |     |                       | which are herein incorporated by        | disorders and pre-neonlastic            |
|     |         |     |                       | reference in its entirety. T cells that | conditions such as for example          |
|     |         |     |                       | may be used according to these          | hynemiasia metanjasia and/or            |
|     |         |     |                       | assays are publicly available (e.g.,    | dysplasia. Preferred indications        |
|     |         |     |                       | through the ATCCTM). Exemplary          | also include anemia, pancytopenia,      |
|     |         |     |                       | human T cells that may be used          | leukopenia, thrombocytopenia,           |
|     |         |     |                       | according to these assays include the   | Hodgkin's disease, acute                |
|     |         |     |                       | JURKAT cell line, which is a            | lymphocytic anemia (ALL),               |
|     |         |     |                       | suspension culture of leukemia cells    | plasmacytomas, multiple myeloma,        |
|     |         |     |                       | that produce IL-2 when stimulated.      | Burkitt's lymphoma, arthritis, AIDS,    |
|     |         |     |                       |                                         | granulomatous disease, inflammatory     |
|     |         |     |                       |                                         | bowel disease, sepsis, neutropenia,     |
|     |         |     |                       |                                         | neutrophilia, psoriasis, suppression    |
|     |         |     |                       |                                         | of immune reactions to transplanted     |
|     |         |     |                       |                                         | organs and tissues, hemophilia,         |
|     |         |     |                       |                                         | hypercoagulation, diabetes mellitus,    |
|     |         |     |                       |                                         | endocarditis, meningitis, Lyme          |
|     |         |     |                       |                                         | Disease, asthma and allergy.            |
|     | HNHOD46 | 571 | Activation of         | This reporter assay measures            | Highly preferred indication includes    |
| 167 |         |     | transcription through | activation of the NFkB signaling        | allergy, asthma, and rhinitis.          |
|     |         |     | NFKB response         | pathway in Ku812 human basophil         | Additional highly preferred             |
|     |         |     | element in immune     | cell line. Assays for the activation of | indications include infection (e.g., an |
|     |         |     | cells (such as        | transcription through the NFKB          | infectious disease as described below   |
|     |         |     | basophils).           | response element are well-known in      | under "Infectious Disease"), and        |
|     |         |     |                       | the art and may be used or routinely    | inflammation and inflammatory           |
|     |         |     |                       | modified to assess the ability of       | disorders. Preferred indications        |
|     |         |     |                       | polypeptides of the invention           | include immunological and               |
|     |         |     |                       | (including antibodies and agonists or   | hempatopoietic disorders (e.g., as      |
|     |         |     |                       | antagonists of the invention) to        | described below under "Immune           |
|     |         |     |                       | regulate NFKB transcription factors     | Activity", and "Blood-Related           |
|     |         |     |                       | and modulate expression of              | Disorders"). Preferred indications      |
|     |         |     |                       | immunomodulatory genes.                 | also include autoimmune diseases        |
|     |         |     |                       | Exemplary assays for transcription      | (e.g., rheumatoid arthritis, systemic   |
|     |         |     |                       | through the NFKB response element       | lupus erythematosis, multiple           |
|     |         |     |                       | that may be used or rountinely          | sclerosis and/or as described below)    |

| and immunodeliciencies (e.g., as and and immunodeliciencies (e.g., as indicated below). Performed indications also include tooplastic diseases (e.g., localiumi, laypidoma, medianoma, and ora se described below mader "Hyperpolicitative Diseasedes"). Preferred indications and one "Physiolicitative Diseasedes"). Preferred indications and indicate tooplastics and easers, and the companion, and prostact, breast, lung, colon, pancrettic, breast, lung, colon, pancrettic, breast, lung, colon, pancrettic, urimay uned cancers and as described below under "Hyperprolificative Disearders".                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Highly preferred indications include reophastic diseases (e.g. Hermit, hyphomota, and/or as described below under estable pleow under "Hyperproliferative Disorders")  "Hyperproliferative Disorders")  Highly preferred indications include morphisms and entores, such as, for example, leukeruni, lymphoma (e.g., Teell lymphoma, Burktif's French Pumphoma, Hurktif's hymphoma, Herdgiff's disease), hymphoma, Herdgiff's disease).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| modified to test NFKB-response<br>teneral activity of polypepides of<br>the invention (including authorities<br>and goinstso or mappoils of the<br>invention (including authorities<br>invention) leidude assays disclosed in<br>invention) leidude assays disclosed in<br>perger et al., Groot 66:61-10 (1989;<br>Cullen and Malin, Methods in<br>Tayanna) 21 (36-23-886 (1982);<br>Henthorn et al., Proc Natl Acad Sci<br>18-38 85-632-64 (1982); Manmo<br>et al., Int Acta Allergy Immunol<br>et al., Int Acta Allergy Immunol<br>according to these assays include<br>according to the according to the according to the<br>according to the according to the according to the according to the<br>according to the according to the according to the according to the<br>according to the according to the acco | assays for the activation of reassays for the activation of reassarphion through the Commun function Activation Site (GAS) response element are well-known in modified to soasse the ability of polypsprides of the invention of conditional modifieds and agonists or authority and activation alongonists of the invention of the activation o |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Activation of Activation of Graphics of GAS response element in immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| molecularity and accordate because the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | colon paperestic ecophages      | stomach, brain, liver and urinary | cancer. Other preferred indications  | include benign dysproliferative | disorders and pre-neoplastic | conditions, such as, for example, | hyperplasia, metaplasia, and/or       | dysplasia. Preferred indications      | include autoimmune diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below),          | immunodeficiencies (e.g., as    | described below), boosting a T cell- | mediated immune response, and     | suppressing a T cell-mediated | immune response. Additional   | preferred indications include        | inflammation and inflammatory    | disorders. Highly preferred        | indications include blood disorders | (e.g., as described below under | "Immune Activity", "Blood-Related    | Disorders", and/or "Cardiovascular | Disorders"), and infection (e.g., viral | infections, tuberculosis, infections | associated with chronic | granulomatosus disease and | malignant osteoporosis, and/or an | infectious disease as described below | under "Infectious Disease"). An | additional preferred indication is | idiopathic pulmonary fibrosis. | Preferred indications include anemia, | pancytopenia, leukopenia, |
| loo to a serido estado estado estado estado estado estado en estado en estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado estado e | functions Eventnlary assays for | transcription through the GAS     | response element that may be used or | routinely modified to test GAS- | response element activity of | polypeptides of the invention     | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and      | Malm, Methods in Enzymol          | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Matikainen et al.,      | Blood 93(6):1980-1991 (1999); and | Henttinen et al., J Immunol   | 155(10):4582-4587 (1995), the | contents of each of which are herein | incorporated by reference in its | entirety. Exemplary human T cells, | such as the MOLT4 cell line, that   | may be used according to these  | assays are publicly available (e.g., | through the ATCCTM).               |                                         |                                      |                         |                            |                                   |                                       |                                 |                                    |                                |                                       |                           |
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| lymphocytic attentia (ALL), plemphocytic attentia (ALL), plemped comes, multiple myeloma, plemped cyclons, multiple myeloma, diesese, inflammony bowed diesese, sepsis, neutropetia, neutrophilia, psoriais, suppresentia, neutrophilia, psoriais, suppresential, englanded organis and issues, kemophilia, compounditis, memberaditis, lympercoaguliation, diabetes militats, endocarditis, mempilistis, Lympe ordoorearditis, mempilistis, Lympe ordoorearditis, mempilistis, Lympe biseses, and suthma and allergy. | Highly preferred indications include inflammation and includent and includence and inflammation and disorders. Highly preferred indications include blood disorders (e.g., as described below disorders (e.g., as described below to rucked Disorders), "Blood-Radiotal State (Parketts), "Blood-Radiotal Radiotal Radiotal State (Parketts), An additional and/or as described below, An additional medication (e.g., AJDS, and or an infection (e.g., AJDS, and or an infection (e.g., AJDS, and "Blood"), "Blood and "Blood" in mader of the classification (e.g., AJDS, and "Blood"), "Blood as described below under a described below under a described below under a described below in under a described below in under a described below under a described below in discussion is blood in some described below under a described below under a described below under as described below under a described below under a described below under a described below under a described below under a described below under a described below under a described below under a described below under a described below under a described below and canners, such as, for Highly preferred indications include the additional and denterers, such as, for Highly preferred indications include the additional and denterers such as, for the property of the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the additional and the add                                                                                                     |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | transacription through the PIKB<br>stayons electron are well-known in the rat and many be used or routinely<br>modified to assess the ability of oppopperation of the invention) to<br>modified to assess the ability of<br>polypeptides of the invention) to<br>regulate NFB transcription factors and modulate expression of<br>immunomodulatory genes. The expension of<br>regulate NFB transcription factors<br>from the area of the properties of<br>the resemble assists for transcription<br>through the NFGB response element<br>through the NFGB response element<br>and through the NFGB response element<br>and against through the NFGB response element<br>and against through the NFGB response element<br>and against through the NFGB response element<br>and against through the NFGB response element<br>and against through the NFGB response element<br>and against through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through the NFGB response element<br>and through through through through the NF |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | transcription through the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of                                                                                                     |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| extraction, tenkenia, lymphoma, and present between the currinoral tenkenia, lymphoma, and present, breast, lang, colon, and present, breast, lang, colon, panceratic, esophageal, stometh, panceratic, esophageal, stometh, or preferred indications include benign preferred indications include benign morphisms, countinos, such as, for morphism, countinos, such as, for morphism, countinos, such as, for morphism, conditions, such as, for morphism, conditions, such as, for morphism, and or desplasia, metalpois in metalpois and or desplasia, predicted and or desplasia, proposition, included in the morphocyteria, included in the morphocyteria, included in the morphocyteria, included includent, included included in hypocroogalation, diabetes mellins, sometics, the morphism, and altergy. | A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNS alpha production. An allemante highly preferred embodiment of the invention includes a method for simulating (e.g., increasing) TNF alpha production. Preferred alpha production. Preferred indications include blood disorders (e.g., as described below under TNF alpha production. Preferred infinitentions include blood disorders (e.g., as described below under TNF alpha alpha production.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| which are premise of cash of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the MOLT4, human T cells, and as such as the MOLT4 assays are publicly available (e.g., through the ATCC <sup>27</sup> n).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Assays for the activation of<br>transcription through the Serum<br>Response Emeract (SRE) are well-<br>known in the art and may be used or<br>routinely modified to assess the<br>ability of polypeptides of the<br>invention (including antibodies and<br>againsist or antagoniss of the<br>against or antagoniss of the<br>revention) to regulate serum<br>response factors and modulate the<br>response factors and modulate the<br>regulations are modulated the regulations and modulate the<br>regulations are also and modulate the regulations are also as a second<br>property of the property of the property of the property of the<br>property of the property of the |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Activation of reasonable transcription through serum response element in immune cells (such as natural killer cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 571                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| Disorders"). Highly preferred disorders is included into included included into included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included included incl | immune response, Additional highly preterred independent information and information information and information and information and information and information and information and information and information and information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the information in the informati | morphasms and canaers, such as, for<br>memoria, furname, lymphoma,<br>melanoma, glioma (e.g., malignant<br>glioma, solid tumors, and prostace,<br>breast, lung, colon, panceratic,<br>berast, lung, colon, panceratic,<br>berast, lung, colon, panceratic,<br>depoplageal, storach, berain, liver and<br>utimay canaer. Other preferred<br>dosproiferative disorders and pre-<br>neoplastic conditions, such as, for<br>resorbishis, memplasia, menaplasia,<br>andro dysplasia. Preferred<br>andred designations, and and pre-<br>lated are presented as and pre-<br>neoplastic conditions, such as, for<br>example, hyperplasia, metaplasia,<br>andro dysplasia. Preferred<br>functions included aremini,<br>plancytoperia, lettkoperia, |
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| of growth-related genes in many cell type. Exemples seasos for transcription through the SRB that may be used or noutlierly modified to test SRB extivity of the polypeptides of the invention (clickaling autholics and ageniss or antagoniss of the polymented of the invention (clickaling autholics and ageniss or antagoniss of the invention) include seasys inclosed in prevention) include seasys inclosed in the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the contraction of the co | Cluden and Mathi, Methods in<br>Fragma, 156:362-368 (1992);<br>Hendmen et al., Proc Natl Acad Sci<br>USA, 85:634-6346 (1988); Benson<br>et al., Immunol 153(9):386-2873<br>(1994); and Blate et al., Vitus Genes<br>12(2):105-117 (1997), the content of<br>incorporated by reference in its<br>entirety. T cells that may be used<br>accounting to these susyas are publicly<br>available (e.g., through the<br>ATCCON). Exemplan T Cells that<br>may be used according to these                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | assays include the NR-YT cell line,<br>which is human natural killer cell<br>which the proposite and cytotoxic<br>activity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|   |     |                        |                                        | thrombocytopenia, Hodgkin's           |
|---|-----|------------------------|----------------------------------------|---------------------------------------|
| _ |     |                        |                                        | disease, acute lymphocytic anemia     |
|   |     |                        |                                        | (ALL), plasmacytomas, multiple        |
|   |     |                        |                                        | myeloma, Burkitt's lymphoma,          |
| _ |     |                        |                                        | arthritis, AIDS, granulomatous        |
|   |     |                        |                                        | disease, inflammatory bowel disease,  |
| _ |     |                        |                                        | neutropenia, neutrophilia, psoriasis, |
| _ |     |                        |                                        | suppression of immune reactions to    |
| _ |     |                        |                                        | transplanted organs and tissues,      |
| _ |     |                        |                                        | hemophilia, hypercoagulation,         |
| _ |     |                        |                                        | diabetes mellitus, endocarditis,      |
| _ |     |                        |                                        | meningitis, Lyme Disease, cardiac     |
|   |     |                        |                                        | reperfusion injury, and asthma and    |
| _ |     |                        |                                        | allergy. An additional preferred      |
| _ |     |                        |                                        | indication is infection (e.g., an     |
|   |     |                        |                                        | infectious disease as described below |
| _ |     |                        |                                        | under "Infectious Disease").          |
| Н | 571 | Activation of          | Assays for the activation of           | Highly preferred indications          |
|   |     | transcription through  | transcription through the NFKB         | include inflammation and              |
|   |     | NFKB response          | response element are well-known in     | inflammatory disorders. Highly        |
| _ |     | element in immune      | the art and may be used or routinely   | preferred indications include blood   |
| _ |     | cells (such as natural | modified to assess the ability of      | disorders (e.g., as described below   |
| _ |     | killer cells).         | polypeptides of the invention          | under "Immune Activity", "Blood-      |
| _ |     |                        | (including antibodies and agonists or  | Related Disorders", and/or            |
|   |     |                        | antagonists of the invention) to       | "Cardiovascular Disorders"). Highly   |
| _ |     |                        | regulate NFKB transcription factors    | preferred indications include         |
| _ |     |                        | and modulate expression of             | autoimmune diseases (e.g.,            |
| _ |     |                        | immunomodulatory genes.                | rheumatoid arthritis, systemic lupus  |
| _ |     |                        | Exemplary assays for transcription     | erythematosis, multiple sclerosis     |
| _ |     |                        | through the NFKB response element      | and/or as described below), and       |
| _ |     |                        | that may be used or rountinely         | immunodeficiencies (e.g., as          |
| _ |     |                        | modified to test NFKB-response         | described below). An additional       |
| _ |     |                        | element activity of polypeptides of    | highly preferred indication is        |
| _ |     |                        | the invention (including antibodies    | infection (e.g., AIDS, and/or an      |
| _ |     |                        | and agonists or antagonists of the     | infectious disease as described below |
| _ |     |                        | invention) include assays disclosed in | under "Infectious Disease").          |
| _ |     |                        | Berger et al., Gene 66:1-10 (1998);    | Highly preferred indications include  |

|                                                                           |                                       |                                                                     |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                     |                                   |                                       |                                        |                                      |                               |                          |                           |                                  |                                   | -                                    |
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| Disorders", and/or "Blood-Related<br>Disorders"), and infection (e.g., an | infectious disease as described below | under infectious Disease ), ruginy<br>preferred indications include | autoimmune diseases (e.g.,           | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below) and | immunodeficiencies (e.g., as          | described below). Additional highly   | preferred indications include      | inflammation and inflammatory   | disorders. Highly preferred | indications also include neoplastic  | diseases (e.g., leukemia, lymphoma, | and/or as described below under      | "Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as,    | leukemia, lymphoma, prostate,       | breast, lung, colon, pancreatic,      | esophageal, stomach, brain, liver,   | and urinary cancer. Other preferred | indications include benign     | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred           | indications include arthritis, asthma, | AIDS, allergy, anemia, pancytopenia, | leukopenia, thrombocytopenia, | Hodgkin's disease, acute | lymphocytic anemia (ALL), | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, granulomatous | disease, inflammatory bowel disease, |
| (including antibodies and agonists or<br>antagonists of the invention) to | modulate growth and other cell        | transcription through the AP1                                       | response element that may be used or | routinely modified to test AP1-      | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1988); Cullen and | Malm, Methods in Enzymol    | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Rellahan et al., J Biol | Chem 272(49):30806-30811 (1997); | Chang et al., Mol Cell Biol          | 18(9):4986-4993 (1998); and Fraser | et al., Eur J Immunol 29(3):838-844 | (1999), the contents of each of which | are herein incorporated by reference | in its entirety. Human T cells that | may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary      | human T cells that may be used    | according to these assays include the | SUPT cell line, which is an IL-2 and   | IL-4 responsive suspension-culture   | cell line.                    |                          |                           |                                  |                                   |                                      |
|                                                                           |                                       |                                                                     |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                     |                                   |                                       |                                        |                                      |                               |                          |                           |                                  |                                   |                                      |
|                                                                           |                                       |                                                                     |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                     |                                   |                                       |                                        |                                      |                               |                          |                           |                                  |                                   |                                      |
|                                                                           |                                       |                                                                     |                                      |                                      |                                   |                                |                                       |                                       |                                    |                                 |                             |                                      |                                     |                                      |                                  |                                      |                                    |                                     |                                       |                                      |                                     |                                |                                      |                                     |                                   |                                       |                                        |                                      |                               |                          |                           |                                  |                                   |                                      |

| sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                                                                                                                    | reasons for the activities of irranscription frough the CD38 response element are well-known in modificat on weel-known in modificat to weel from the well-known in modificat to weel from the well-known in modificat to week of the investion of including antibodies and sponiss or amagonies of the investion to similate it. 2 expression in T cells. The company of the company of the investion of similate it. 2 expression in T cells. The company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the compa |
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|                                                                                                                                    | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| immune response. Highly<br>preferred indications include               | neoplastic diseases (e.g., melanoma,<br>renal cell carcinoma, leukemia, | lymphoma, and/or as described | below under "Hyperproliferative | Disorders"). Highly preferred | indications include neoplasms and | cancers, such as, for example, | melanoma (e.g., metastatic | melanoma), renal cell carcinoma | (e.g., metastatic renal cell | carcinoma), leukemia, lymphoma | (e.g., T cell lymphoma), and prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver and | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. A highly | preferred indication includes | infection (e.g., AIDS, tuberculosis, | infections associated with | granulomatous disease, and | osteoporosis, and/or as described | below under "Infectious Disease"). | A highly preferred indication is | AIDS. Additional highly preferred | indications include suppression of | immune reactions to transplanted | organs and/or tissues, uveitis, | psoriasis, and tropical spastic | paraparesis. Preferred indications | include blood disorders (e.g., as | described helow under "Immune |
|------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------|---------------------------------|-------------------------------|-----------------------------------|--------------------------------|----------------------------|---------------------------------|------------------------------|--------------------------------|----------------------------------------|----------------------------------|---------------------------------------|---------------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------------------------------|----------------------------|-------------------------------|--------------------------------------|----------------------------|----------------------------|-----------------------------------|------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|---------------------------------|---------------------------------|------------------------------------|-----------------------------------|-------------------------------|
| that may be used according to these assays include the SUPT cell line, | which is a suspension culture of IL-2 and IL-4 responsive T cells.      | •                             |                                 |                               |                                   |                                |                            |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     |                                     |                                   |                            |                               |                                      |                            |                            |                                   |                                    |                                  |                                   |                                    |                                  |                                 |                                 |                                    |                                   |                               |
|                                                                        |                                                                         |                               |                                 |                               |                                   |                                |                            |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     |                                     |                                   |                            |                               |                                      |                            |                            |                                   |                                    |                                  |                                   |                                    |                                  |                                 |                                 |                                    |                                   |                               |
|                                                                        |                                                                         |                               |                                 |                               |                                   |                                |                            |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     |                                     |                                   |                            |                               |                                      |                            |                            |                                   |                                    |                                  |                                   |                                    |                                  |                                 |                                 |                                    |                                   |                               |
|                                                                        |                                                                         |                               |                                 |                               |                                   |                                |                            |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     |                                     |                                   |                            |                               |                                      |                            |                            |                                   |                                    |                                  |                                   |                                    |                                  |                                 |                                 |                                    |                                   |                               |
|                                                                        |                                                                         |                               |                                 |                               |                                   |                                |                            |                                 |                              |                                |                                        |                                  |                                       |                                 |                            |                                     |                                     |                                   |                            |                               |                                      |                            |                            |                                   |                                    |                                  |                                   |                                    |                                  |                                 |                                 |                                    |                                   |                               |

| нинорее | 145 | Activation of transcription of transcription through (GAS response element in firmanne cells (such as T-cells). | Assays for the activation of transcription through the Gamma Inferient Activation (Sie (GAS)) response element are vell-known in the fact and may be used or routinely modified to assess the ability of polypeptides of the invention of                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Disorders," Blood Related Disorders," Blood Related Disorders," In and or "Cardiovascular Disorders", Profected indications also include amenia, pancytopenia, plengeria, througheria, throughink, througheria, throughink, throughing, throughink, and the throughing throughing throughing throughing throughing throughing throughing throughing throughing throughing through the decidence include recoplesses and indications include recoplesses and encounters, with we, for example, e., |
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|         |     |                                                                                                                 | antagonists of the invention) not<br>antagonists of the invention) not<br>and antagonists of the invention) of the<br>and of the invention of the antagonists of<br>and motived in a wide variety of call<br>inventions. Exemplary associated<br>incutions. Exemplary associated<br>inventions are according to<br>treascription through the GAS<br>treaspose element altura may be used or<br>routinely modified to test GAS-<br>countedy modified to test GAS-<br>toward and the invention of<br>polypeptides of the invention include<br>antagonists of the invention include<br>antagonists of the invention include<br>Gene 66:1-10 (1998); Callen and<br>Gene 66:1-10 (1998); Callen and | the drivening typioning (e.g., Teell lymphoma, purketin lymphoma, Indekin's lymphoma, Indekin's lymphoma, Indekin's lymphoma, Indekin's lymphoma, Indekin's lideness, melanoma, and prostate, diseases, lung-onlon, pancretin, promit prostate, lung-onlon, pancretin, bremi, liver and unimy-canaer. Other preternes the prostate conditiones in the prostate of syspholificative distorters and precentarity, lyptophists, mentaphissis, deseased, preferred indications include autoimmune indications include autoimmune indications include autoimmune straints, systemic linus errhematosia aftritis, systemic linus errhematosia diritis, systemic linus errhematosia.                                                                                                                                                                                                                                                                                                                                                                      |

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| Malm Methods in Enzymol   multiple sclenosis and/or as described |

| 167 | transcription through    | transcription through the Nuclear       | include blood disorders (e.g., as        |
|-----|--------------------------|-----------------------------------------|------------------------------------------|
|     | NFAT response            | Factor of Activated T cells (NFAT)      | described below under "Immune            |
|     | element in immune        | response element are well-known in      | Activity", "Blood-Related                |
|     | cells (such as T-cells). | the art and may be used or routinely    | Disorders", and/or "Cardiovascular       |
|     |                          | modified to assess the ability of       | Disorders"). Highly preferred            |
|     |                          | polypeptides of the invention           | indications include autoimmune           |
|     |                          | (including antibodies and agonists or   | diseases (e.g., rheumatoid arthritis,    |
|     |                          | antagonists of the invention) to        | systemic lupus crythematosis,            |
|     |                          | regulate NFAT transcription factors     | multiple sclerosis and/or as described   |
|     |                          | and modulate expression of genes        | below), immunodeficiencies (e.g., as     |
|     |                          | involved in immunomodulatory            | described below), boosting a T cell-     |
|     |                          | functions. Exemplary assays for         | mediated immune response, and            |
|     |                          | transcription through the NFAT          | suppressing a T cell-mediated            |
|     |                          | response element that may be used or    | immune response. Additional highly       |
|     |                          | routinely modified to test NFAT-        | preferred indications include            |
|     |                          | response element activity of            | inflammation and inflammatory            |
|     |                          | polypeptides of the invention           | disorders. An additional highly          |
|     |                          | (including antibodies and agonists or   | preferred indication is infection (e.g., |
|     |                          | antagonists of the invention) include   | an infectious disease as described       |
|     |                          | assays disclosed in Berger et al.,      | below under "Infectious Disease").       |
|     |                          | Gene 66:1-10 (1998); Cullen and         | Preferred indications include            |
|     |                          | Malm, Methods in Enzymol                | neoplastic diseases (e.g., leukemia,     |
|     |                          | 216:362-368 (1992); Henthorn et al.,    | lymphoma, and/or as described            |
|     |                          | Proc Natl Acad Sci USA 85:6342-         | below under "Hyperproliferative          |
|     |                          | 6346 (1988); Serfling et al., Biochim   | Disorders"). Preferred indications       |
|     |                          | Biophys Acta 1498(1):1-18 (2000);       | include neoplasms and cancers, such      |
|     |                          | De Boer et al., Int J Biochem Cell      | as, for example, leukemia,               |
|     |                          | Biol 31(10):1221-1236 (1999);           | lymphoma, and prostate, breast, hmg,     |
|     |                          | Fraser et al., Eur J Immunol            | colon, pancreatic, esophageal,           |
|     |                          | 29(3):838-844 (1999); and Yeseen et     | stomach, brain, liver and urinary        |
|     |                          | al., J Biol Chem 268(19):14285-         | cancer. Other preferred indications      |
|     |                          | 14293 (1993), the contents of each of   | include benign dysproliferative          |
|     |                          | which are herein incorporated by        | disorders and pre-neoplastic             |
|     |                          | reference in its entirety. T cells that | conditions, such as, for example,        |
|     |                          | may be used according to these          | hyperplasia, metaplasia, and/or          |
|     |                          | assays are publicly available (e.g.,    | dysplasia. Preferred indications         |
|     |                          | through the ATCCTM). Exemplary          | also include anemia, pancytopenia,       |

| leukopenia, thrombocytopenia, thogalis is disease, acute lymphocytic amerina (ALL). Houghis is disease, acute lymphocytic amerina (ALL). Burkiti is Jurphoona, arthritis AIDS. Burkiti is Jurphoona, arthritis AIDS. Burkiti is Jurphoona, arthritis AIDS. bowel disease, stripassion to bowel disease, stripassion of of immune reactions to transplanted of grants and tisease, hemophilia, popusa and tisease, hemophilia, lypercoagulation, diabetes mellitas, bypercoagulation, diabetes mellitas, Disease, asthma and altergy. | include inflammation and include inflammation (assected indexing) and include inflammation (assected includes) preferred infortions include blood disorders (e.g., as discribed below under "Immune Activity", "Blood-Redinosal Boothers," and or. "Activity sealers of the Cardiovascular Boothers," and or. Reinted Disorders', Inguly preferred indications include preferred indications include preferred indications include admirits, systemic lupus preferred arthritis, systemic lupus and/or as described below, and antimitie selectoris and/or as described below, and interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in interior of e.g., AIDS, and/or in the e.g., and and and and and and and and and and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| human T cells that may be used according to these saws include the sucording to these saws include the culture of IL-2 and IL-4 responsive T cells.                                                                                                                                                                                                                                                                                                                                                                                  | transcription through the NFRB<br>transcription through the properties of<br>polypeptides of the invention) to<br>an undefined to access the achieves to<br>through the NFRB transcription through<br>the NFRB reports element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through the NFRB response element<br>through through through through through the NFRB response<br>through through the NFRB response element<br>through the NFRB response to<br>through through through through the NFRB res |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Advancin of a characterion of a characterion of a characterion immune cells (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 571                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | нинория                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|     |         |     |                          | al., Virus Gnes 15(2):105-117           | Highly preferred indications include  |
|-----|---------|-----|--------------------------|-----------------------------------------|---------------------------------------|
|     |         |     |                          | 844 (1999), the contents of each of     | as,melanoma, renal cell carcinoma,    |
|     |         |     |                          | which are herein incorporated by        | leukemia, lymphoma, and prostate,     |
|     |         |     |                          | reference in its entirety. T cells that | breast, lung, colon, pancreatic,      |
|     |         |     |                          | may be used according to these          | esophageal, stomach, brain, liver and |
|     |         |     |                          | assays are publicly available (e.g.,    | urinary cancer. Other preferred       |
|     |         |     |                          | through the ATCCTM). Exemplary          | indications include benign            |
|     |         |     |                          | human T cells that may be used          | dysproliferative disorders and pre-   |
|     |         |     |                          | according to these assays include the   | neoplastic conditions, such as, for   |
|     |         |     |                          | SUPT cell line, which is a suspension   | example, hyperplasia, metaplasia,     |
|     |         |     |                          | culture of IL-2 and IL-4 responsive T   | and/or dysplasia. Preferred           |
|     |         |     |                          | cells.                                  | indications also include anemia,      |
|     |         |     |                          |                                         | pancytopenia, leukopenia,             |
|     |         |     |                          |                                         | thrombocytopenia, Hodgkin's           |
|     |         |     |                          |                                         | disease, acute lymphocytic anemia     |
|     |         |     |                          |                                         | (ALL), plasmacytomas, multiple        |
|     |         |     |                          |                                         | myeloma, Burkitt's lymphoma,          |
|     |         |     |                          |                                         | arthritis, AIDS, granulomatous        |
|     |         |     |                          |                                         | disease, inflammatory bowel disease,  |
|     |         |     |                          |                                         | sepsis, neutropenia, neutrophilia,    |
|     |         |     |                          |                                         | psoriasis, hemophilia,                |
|     |         |     |                          |                                         | hypercoagulation, diabetes mellitus,  |
|     |         |     |                          |                                         | endocarditis, meningitis, Lyme        |
|     |         |     |                          |                                         | Disease, suppression of immune        |
|     |         |     |                          |                                         | reactions to transplanted organs,     |
|     |         |     |                          |                                         | asthma and allergy.                   |
|     | HNHOD46 | 571 | Activation of            | Assays for the activation of            | A highly preferred indication is      |
| 167 |         |     | transcription through    | transcription through the Signal        | allergy. Another highly               |
|     |         |     | STAT6 response           | Transducers and Activators of           | preferred indication is asthma.       |
|     |         |     | element in immune        | Transcription (STAT6) response          | Additional highly preferred           |
|     |         |     | cells (such as T-cells). | element are well-known in the art       | indications include inflammation and  |
|     |         |     |                          | and may be used or routinely            | inflammatory disorders.               |
|     |         |     |                          | modified to assess the ability of       | Preferred indications include blood   |
|     |         |     |                          | polypeptides of the invention           | disorders (e.g., as described below   |
|     |         |     |                          | (including antibodies and agonists or   | under "Immune Activity", "Blood-      |
|     |         |     |                          | antagonists of the invention) to        | Related Disorders", and/or            |

| "Cardiovascular Disorders"). Preferred indications include | autoimmme diseases (e.g.,        | rheumatoid arthritis, systemic lupus | erythematosis, multiple selerosis    | and/or as described below) and   | immunodeficiencies (e.g., as     | described below).             | Preferred indications include         | neoplastic diseases (e.g., leukemia,  | lymphoma, melanoma, and/or as      | described below under           | "Hyperproliferative Disorders"). | Preferred indications include        | neoplasms and cancers, such as, | leukemia, lymphoma, melanoma, and | prostate, breast, lung, colon,      | pancreatic, esophageal, stomach,     | brain, liver and urinary cancer. Other | preferred indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for   | example, hyperplasia, metaplasia, | and/or dysplasia.                       | Preferred indications include anemia, | pancytopenia, leukopenia,            | thrombocytopenia, Hodgkin's      | disease, acute lymphocytic anemia   | (ALL), plasmacytomas, multiple     | myeloma, Burkitt's lymphoma,           | arthritis, AIDS, granulomatous    | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, | psoriasis, suppression of immune | reactions to transplanted organs and | tissues, hemophilia, | hypercoagulation, diabetes mellitus, |
|------------------------------------------------------------|----------------------------------|--------------------------------------|--------------------------------------|----------------------------------|----------------------------------|-------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------------|--------------------------------------|---------------------------------|-----------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|-----------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-----------------------------------|--------------------------------------|------------------------------------|----------------------------------|--------------------------------------|----------------------|--------------------------------------|
| regulate STAT6 transcription factors                       | multiple genes. Exemplary assays | for transcription through the STAT6  | response element that may be used or | routinely modified to test STAT6 | response element activity of the | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol         | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Georas et al., Blood | 92(12):4529-4538 (1998); Moffatt et | al., Transplantation 69(7):1521-1523 | (2000); Curiel et al., Eur J Immunol   | 27(8):1982-1987 (1997); and Masuda   | et al., J Biol Chem 275(38):29331-  | 29337 (2000), the contents of each of | which are herein incorporated by  | reference in its entirety. T cells that | may be used according to these        | assays are publicly available (e.g., | through the ATCCTM). Exemplary T | cells that may be used according to | these assays include the SUPT cell | line, which is a suspension culture of | IL-2 and IL-4 responsive T cells. |                                      |                                    |                                  |                                      |                      |                                      |
|                                                            |                                  |                                      |                                      |                                  |                                  |                               |                                       |                                       |                                    |                                 |                                  |                                      |                                 |                                   |                                     |                                      |                                        |                                      |                                     |                                       |                                   |                                         |                                       |                                      |                                  |                                     |                                    |                                        |                                   |                                      |                                    |                                  |                                      |                      |                                      |
|                                                            |                                  |                                      |                                      |                                  |                                  |                               |                                       |                                       |                                    |                                 |                                  |                                      |                                 |                                   |                                     |                                      |                                        |                                      |                                     |                                       |                                   |                                         |                                       |                                      |                                  |                                     |                                    |                                        |                                   |                                      |                                    |                                  |                                      |                      |                                      |
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|    |          |     |                                                                                                                 |                                                                                                                                                                                              | endocarditis, meningitis, and Lyme<br>Disease. An additional<br>preferred indication is infection (e.g.,<br>an infectious disease as described<br>below moder "Infections Disease")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| 89 | IINTB126 | 572 | Production of II-8 by Production of II-8 by Production of the Coord is frame Unibilized Cond Endodreini Cells). | are very likewing in the art and may be used or routinely modificate to assess invention of including antibodies and invention (including antibodies and and and and and and and and and and | Highly preferred indications include disorders for the mannovogeta and not intermating disorders (e.g., south as at lengty, and mannovogeta and not intermated disorders (e.g., south as the first production of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the con |
|    | HNTBI26  | 572 | Regulation of apoptosis                                                                                         | macrophages, and lymphocytes.  Caspase Apoptosis. Assays for                                                                                                                                 | A highly preferred indication is                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| diabetes mellitus.  An additional highly preferred indication is a compileation associated with diabetes (e.g., diabetic retinopathy, diabetes (e.g., diabetic retinopathy, ediabetic nephropathy, kidney disease (e.g., remal failure nenhromathy entrol failure nenhromathy. | e., treat antiant, repropients and other control disorders as according to Recent Disorders as section below, district morphy, disorders better disease and incre demagnetic e.g., due to disbetic neuropathy, blood vessel blockage, heart disease, and the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion of the dispersion | onthistin, dowsiness, motted the dowledge, seatons, mental conthistion, dowsiness, motted occur, and approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately approximately | Howomen Disposers section below), neuropathy, vision below), neuropathy, vision maintainent (eg., diabetic retinopathy and blindness), ulores and impairon (e.g., mitchious dissesses and disorders as described in the "Infections as presses and disorders as described in the "Infections as flowers" section below, especially of the turnary tract and skin), carpal turned syndrome and Dapaytren's Am additional unruel syndrome and Dapaytren's highly preferred indication is obesity. |
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| caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or attaconists of the invention).                                                                  | angulacs or terration) to<br>promote capese protease-mediated<br>propress, Appoints in paracentic<br>beta is associated with induction and<br>progression of diabetes. Exemplary<br>assays for capase apoptosis that may<br>be used or multirely modified to test<br>on the progression of the properties of the<br>propersistics of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | including antibotics and agoinsts or antiagonists of the invention) include an assignation include the assays discloder in Lowelt, AC, et al., EBS, Lett. 400(1), 2004. Set al., Booken Mol Biol Int. 39(6), 1229-36 (1996).  129(4) 567 a. d. B. The Thermanol, 129(4) 567 a. d. B. Thermanol, 129(4) 567 a. d. B. Thermanol, 129(4) 567 a. d. B. Thermanol, 129(4) 567 a. d. B. Thermanol, 129(4) 567 a. d. Martin, International Color, 139 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 129(4) 567 a. d. Martin, 1 | 14 FIDS Left, 244/21354-24,<br>1999); Zhang, S., et al., FEBS Leu,<br>1995); Zhang, S., et al., FEBS Leu,<br>1995); 122-150 (2000);<br>Nort et al., J Vasc Res 37(3); 299-218<br>2000), and Karsan and Heltun, J<br>Atherweder Thromb 3(2); 7-80<br>Atherweder Thromb 3(2); 7-80<br>are bleepin incorporated by reference<br>in its entirety. Panervatic cells that<br>are bleepin incorporated by reference<br>in its entirety. Panervatic cells that<br>are bened according to these          |
| in pancreatic beta cells.                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| 168                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| and/or complications associated with obesity. Additional highly preferred indications include weight fast of additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | A highly preferred indication is diabetes mellinas.  A diabetes mellinas.  B diadunan lighty perferred indication is a complication associated with diabetes (e.g., diabetic retinopally, diabetic repinopally, idiabetic repinopally, idiabetic mellinopally, idiabetic mellinopally, idiabetic mellinopally, idiabetic mellinopally, indiabetic mellinopally, indiapetic mellinopally, indiapetic and diabetic neuropally, nerve diseases and diseathers as described on the 'Renail Disonders' success and nerve diamage. Cat, also to diabetic neuropally, perve diseases and nerve diamage. Bloode versel bloodege, heart disease, and continson, downsiers, quovasiness, another of diabetic neuropally or blood versel bloodege, serizures, mental continson, downsiers, and continson, downsiers, and continson, downsiers, and continson, downsiers, and continson, downsiers, and diabetic neuropally or blood versel diabetic neuropally or blood versel bloodege, serizures, mental cisease, and diabetic disease, hypertension, stroke, and other diseases, preferrension, stroke, and other diseases in petrension. |
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| through the ATCC'N and/or may be routinely generated. Exemplary parteredic cells that may be used according to these seasys include RN-m. (RN-m) is not addrected. RN-m. (RN-m) is not addrected. The control of the many and and according to the seasy include RN-m. (RN-m) is not addrected. In the cells produce and search is left cell tumor. The cells produce and search is left cell tumor, and produce insulin, sommostanti, and possibly dependent and the cells produce and search is a forth of the cells and the cells produce and search is a forth of the cells and the cells produce and search is a forth of the cells and the cells and the cells are considered as a forth of the cells and the cells are cells are cells and the cells are cells are cells and the cells are cells are cells are cells and the cells are  caspase apoptosis are well known in caspase apoptosis are well known in meditar and map be used or nontracy modified to assess the ability of polypeptides of the invention of relimining amplies and agoniss or antagonists of the invention) to anone caspase to the invention) to anone caspase to the invention) to apoptosis. Apoptosis in panceatic apoptosis, Apoptosis in panceatic apoptosis, Apoptosis in panceatic apoptosis, Apoptosis in panceatic apoptosis, Apoptosis in panceatic apoptosis, Apoptosis in panceatic apoptosis, assays for eages apoptosis in the accordance apoptosis and apoptosis of distribution and progression of diabeters. Exemplary be used or rouninely modified to test polyperpidics of the invention included the assays disclosed in: Loweth, Ac., et al., EBS Lett. 4040(3): Sani, KS, et al., Brochem Mei Bult, apple 1229-36 (1996); Kantilerin, A., et al., BrJ Planmaool.                                                                                                                                                                                                       |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 573                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|     |         |     |                                                | al, Diabetes, 50 Suppl 1: S447-7<br>(1900); Salk Ke, at J. Immunol, 1600); Salk Ke, at J. Immunol, 1600(7); Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, Salk Ke, | reflections as described in the foreign described in the foreign was described in the disorders' section disorders' section disorders' described in the disorder's section disorders' section below), remorpathy, vision below), remorpathy, vision mapaired to disorders and impaired to disorders and impositor of expendition of the disorders and impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impositor of the impo |
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| 169 | HNTBL27 | 573 | Production of IL-10 and activation of T-cells. | Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-"Immune Activity", and "Blood-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| aganists or antagonass of the mivention) to simulate or inhibit disproportion of II. John and or activation system to a seases the ability of polyaperides and in answerie used or routinely modified to an assess the ability of polyaperides and in answerie or including the appoints or antagonists of the my control (including my control or and the polyaperides and individual or production and/or T-cell proliferation in production and/or T-cell proliferation in include, for example, assays such as the seed of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of | A highly preferred embodiment of      | TNFa FMAT. Assays for                                        | Production of TNF | 574 | HNTCE26 |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | under Th2 polarizing conditions                              |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | and asthma. Primary I helper 2                               |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | initiation and pathogenesis of allergy                       |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | cells play a major role in the                               |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | differentiation and activation of Th2                        |                   |     | _       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | IL5 and IL6. Factors that induce                             |                   |     | _       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | T cells that secrete IL4, IL10, IL13,                        |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | activation. Th2 cells are a class of                         |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | measured as a marker of Th2 cell                             |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | secreted from Th2 cells may be                               |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | assays include Th2 cells. IL10                               |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | may be used according to these                               |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | their entirety. Exemplary cells that                         |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | herein incorporated by reference in                          |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | the contents of each of which are                            |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | Therapeutics; 88: 187-196 (2000);                            |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | for asthma" Pharmacology &                                   |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | helper type 2 cell-directed therapy                          |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | 968 (2000), and Cohn, et al., "T-                            |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | disease" Br Med Bull; 56 (4): 956-                           |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | DS, et al., "Th-2 cytokines in allergic                      |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | disclosed and/or cited in: Robinson,                         |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       | include, for example, assays such as                         |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | immune response.                      | production and/or T-cell proliferation                       |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | suppressing a T cell-mediated         | invention) to modulate IL-10                                 |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | mediated immune response, and         | agonists or antagonists of the                               |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | described below), boosting a T cell-  | antibodies of the invention (including                       |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | immunodeficiencies (e.g., as          | assess the ability of polypeptides and                       |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and/or as described below),           | may be used or routinely modified to                         |                   |     |         |
| bit<br>tivation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Crohn"s disease, multiple sclerosis   | of T-cells. Exemplary assays that                            |                   |     |         |
| bit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | systemic lupus erythematosis,         | production of IL-10 and/or activation                        |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | diseases (e.g., rheumatoid arthritis, | invention) to stimulate or inhibit                           |                   |     |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Related Disorders"), autoimmune       | agonists or antagonists of the                               |                   |     | ⊢       |

| the invention includes a method for inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embediment of the invention includes a method for simulating (e.g., inversing) FNF alpha production. Highly preferred embediment of the invention includes a method for simulating (e.g., invention). | indications include blood disorders are appropriated in regarding the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of | described below), boosting a T cell-<br>mediced immune response, and<br>suppressing a T cell-mediated, and<br>manner response. Additional highly<br>preferred indications include<br>preferred indications include disaments<br>disorders, and treating joint damage<br>in patients with rheumanial arthritis.<br>An additional highly preferred<br>indication is sepsis. Highly<br>preferred indications included<br>indexation is desired indications included<br>no polyastic diseases (e.g., lethernia, | lymphoma, and/or as described<br>below under Hypperproliferative<br>Disorders"). Additionally, highly<br>preferred indications include<br>neoplasms and cancers, such as,<br>leukemia, lymphoma, melanoma,<br>glioma (e.g., malignant gliona).        |
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| immunomodulatory proteins produced by activated macrophages, T cells, ifrobbasis, smoth musele, and other cell types that exer a wide variety of inflammatory and eytotoxic efficies on a variety of cells eytotoxic efficies on a variety of cells ext well browen in the ort and most be                                    | we ver notwork must at non may to we were notwork must at non may to used or routinely modified to assess the while of popperdies of the invention (including antibodies of the invention (including antibodies of the invention) to mediate inventions to mediate inventions to mediate inflammation and eyototoxicity. Secreptials assess that test for immunomediating proteins evaluate the immunomediating proteins evaluate the production of cytokians such as more recorsis feature after.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | and the induction or inhibition of m, minimum or or cytoxoxic response. Such assays that may be used or mentionly medical to test immunomodulatory activity of polypedies of the invention (medicing ambedies and agonists or aurageorists of the invention) include assays disclosed in Minglin et al., 19 Biomodecular Screening 4:193-4 (1993), good (1993), good (1993), good (1993), good (1993), good (1993), good (1993), good (1993), are practical approach*                                       | Chapter 6:138-160 (2000);<br>Verhasset et al., Fara I Immunol<br>28(1);386-3890 (1198); Dahlen et<br>al., J Immunol 160(7);358-3593<br>(1988); Verhasselt et al., J Immunol<br>158:2919-2925 (1997); and Nardelli<br>et al., J Leukoo Biol 65:822-828 |
| alpha by dendritic cells                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                       |
| 170                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                       |

|     |         |     |                                                              | They) the contrasts of each of which are berein incorporated by reference in section of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties | lung, colon, prostate, breast, lung, colon, paracteric, esophiageal, search, brain, liver and trimage cancer. Other preferred indications include benign obsprohistenic edocultions, such as, for example, benign obsprohisten, and or obsplasia, and or obsplasia, and or obsplasia, and or obsplasia, mador and or obsplasia, brediered indications in preparaction and colon of supplement, thrombocytopenia, subritis, AIDS, Burkit's lymborna, arthrifts, AIDS, bowed disease, indure posteristic in preparaction for immune reductions to brasplanted organs and itsuses, knomphilia, poeriasis, suppression of immune reduction to brasplanted nitration is sinfection disease and saltum and allergy. An and saltum and allergy. An infectious disease assertived below under "infectious issuese"). |
|-----|---------|-----|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 170 | HNTCE26 | 574 | Strmulation of insulin secretion from pancreatic beta cells. | sugasy for measuring secretion of<br>insulin are well-known in the art and<br>nearly the used or routinely modified to<br>saces the ability of polypepidies of<br>the invention (including ambodies<br>to the invention of the properties of the<br>invention) to simulate insulin<br>invention; to simulate insulin<br>secretion; for example, insulin<br>secretion is measured by PMAT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | A highly preferred indication is<br>diabetes mellins<br>additional highly preferred indication<br>is complication associated with<br>diabetes (e.g., diabetic retinopathy,<br>diabetes (e.g., timbetic retinopathy,<br>diese to pulpopathy, kithey disease<br>(e.g., renal failure, nephropathy<br>indication other diseases and diseateders as<br>described in the "Renal Disoatders"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

|                                                   | ľ                                                       |                                        |
|---------------------------------------------------|---------------------------------------------------------|----------------------------------------|
| tishing anti-rat mannin anti-ource                |                                                         | section below), dianetic includingly,  |
| Insulin secretion from pancreatic beta            | g<br>g                                                  | nerve damage                           |
| cells is upregulated by glucose and               |                                                         | etic neuropathy),                      |
| also by certain proteins/peptides, and            | _                                                       | blood vessel blockage, heart disease,  |
| disregulation is a key component in               | it in stroke, impotence (e.g., due to                   | e.g., due to                           |
| diabetes. Exemplary assays that may               | _                                                       | diabetic neuropathy or blood vessel    |
| be used or routinely modified to test             | test   blockage), seizures, mental                      | es, mental                             |
| for stimulation of insulin secretion              |                                                         | iness, nonketotic                      |
| (from pancreatic cells) by                        | hyperglycemic-hy                                        | hyperglycemic-hyperosmolar coma,       |
| polypeptides of the invention                     | cardiovascular disease (e.g., heart                     | sease (e.g., heart                     |
| (including antibodies and agonists or             | sts or   disease, atherosclerosis,                      | erosis,                                |
| antagonists of the invention) include             | _                                                       | microvascular disease, hypertension,   |
| assays disclosed in: Ahren, B., et al.,           | et al.,   stroke, and other diseases and                | diseases and                           |
| Am J Physiol, 277(4 Pt 2):R959-66                 | -66 disorders as described in the                       | ribed in the                           |
| (1999); Li, M., et al., Endocrinology,            | _                                                       | "Cardiovascular Disorders" section     |
| 138(9):3735-40 (1997); Kim, K.H.,                 | <ul> <li>H., below), dyslipidemia, endocrine</li> </ul> | mia, endocrine                         |
| et al., FBBS Lett, 377(2):237-9                   | disorders (as described in the                          | ribed in the                           |
| (1995); and, Miraglia S et. al.,                  | "Endocrine Disorders" section                           | ders" section                          |
| Journal of Biomolecular Screening,                | ing,   below), neuropathy, vision                       | hy, vision                             |
| 4:193-204 (1999), the contents of                 | _                                                       | impairment (e.g., diabetic retinopathy |
| each of which is herein incorporated              | _                                                       | and blindness), ulcers and impaired    |
| by reference in its entirety.                     |                                                         | wound healing, and infection (e.g.,    |
| Pancreatic cells that may be used                 | _                                                       | infectious diseases and disorders as   |
| according to these assays are publicly            | _                                                       | Infectious                             |
| available (e.g., through the ATCC <sup>TM</sup> ) | _                                                       | Diseases" section below, especially    |
| and/or may be routinely generated.                |                                                         | of the urinary tract and skin), carpal |
| Exemplary pancreatic cells that may               | _                                                       | tunnel syndrome and Dupuytren's        |
| be used according to these assays                 | _                                                       | An additional                          |
| include rat INS-1 cells. INS-1 cells              | _                                                       | highly preferred indication is obesity |
| are a semi-adherent cell line                     | _                                                       | and/or complications associated with   |
| established from cells isolated from              | _                                                       | obesity. Additional highly preferred   |
| an X-ray induced rat transplantable               | thle indications include weight loss or                 | le weight loss or                      |
| insulinoma. These cells retain                    | alternatively, weight gain                              | ght gain.                              |
| characteristics typical of native                 | Aditional highly preferred                              | preferred                              |
| pancreatic beta cells including                   |                                                         | mplications                            |
| glucose inducible insulin secretion.              | ion. associated with insulin resistance.                | sulin resistance.                      |
| References: Asfari et al.                         |                                                         |                                        |

|                             | referred embodiments of the invention include using polypeptides of the invention of an ambodies, agonais, or antagonists thereof) in decidential, adjustices, prevention, and or recurrent of Inflammation, Vascular Disease, Alprevosclerosis, Restensis, and Stroke                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | A highly perfected embediment<br>of the invention includes a method<br>the invention includes a method<br>proliferation. An alternative highly<br>preferred embediment of the<br>inhibiting adhocyte proliferation.<br>In the preferred embediment of the<br>inhibiting adhocyte proliferation.<br>A highly preferred embediment of<br>the invention includes a method for<br>manufactured to the proposed inferentiation.<br>An alternative bindry preferred    |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Endocrinology 1992 130:167. | LCAM-1 are well-known in the art meaning expression of TCAM-1 are well-known in the art modified to assess the ability of properpides of the invention of including analyses and agoniss or manageniss of the invention in regulate (TCAM-1 expression to regulate (TCAM-1 expression to regulate (TCAM-1 expression to regulate (TCAM-1 expression to the asset of a transpersor or variance) to reactive the art may be used or variance and the asset of a transpersor or variance from the asset of the art may be used or variance and the asset of the art may be used to the art may be used to the art may be used according to these assets as transplic (e.g., through the ATCCPs) and/or may be routifiedy generated. Been according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to these assets include according to the according to | there assay, Kinea essays, for example an Elle. Limes essay, for ERR Sgand transduction that regulate cell proliferation or differentiation are well known in the art and may be add or rountingly modified to assess the ability of polypeptides of the agentist or antageous and of the agentists or antageous or of the muterion (in the duting antibodies and agonists or antageous or of the muterion) to promote or inhibit cell molification, activation, |
|                             | Production of ICAM-1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Activation of Adipocyte BRK Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                    |
| _                           | 574                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 575                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                             | HNTCF26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HNTNC20                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                             | 170                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 171                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Γ    |                                                                               |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  | _                             |
|------|-------------------------------------------------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|-------------------------------|
| - 1- | includes a method for inhibiting                                              | adipocyte differentiation. A      | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immme      | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | dishere mellime An additional |
|      | differentiation. Exemplary assays for<br>FRK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                               |
|      |                                                                               |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                               |
|      |                                                                               |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  | _                             |
|      |                                                                               |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                               |

| highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional |
|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|---------------------------------------|------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|
|                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |
|                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |
|                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                       |                                    |                                        |                                 |                                     |

| 576 Regulation of transcription via DMEET responses chement in adjoncytes and pre-adjoncytes | transcription through the DMIP disheven transcription through the DMIP disheves mellins. Additional light the and may be used or mountable to employ the art and may be used or mountable completeness associated with conferences or fairless regulated with cohyrentiess of the invention disheven the conductive transcription of the invention of the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the present and the pres |
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| le le le le le le le le le le le le le l                                                     | 10 276 S76                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| (including antibodies and agonists or | (e.g., renal failure, nephropathy      | _ |
|---------------------------------------|----------------------------------------|---|
| antagonists of the invention) to      | and/or other diseases and disorders as |   |
| activate the DMEF1 response           | described in the "Renal Disorders"     |   |
| element in a reporter construct (such | section below), diabetic neuropathy,   |   |
| as that containing the GLUT4          | nerve disease and nerve damage         |   |
| promoter) and to regulate insulin     | (e.g., due to diabetic neuropathy),    |   |
| production. The DMEF1 response        | blood vessel blockage, heart disease,  |   |
| element is present in the GLUT4       | stroke, impotence (e.g., due to        |   |
| promoter and binds to MEF2            | diabetic neuropathy or blood vessel    |   |
| transcription factor and another      | blockage), seizures, mental            |   |
| transcription factor that is required | confusion, drowsiness, nonketotic      |   |
| for insulin regulation of Glut4       | hyperglycemic-hyperosmolar coma,       |   |
| expression in skeletal muscle.        | cardiovascular disease (e.g., heart    |   |
| GLUT4 is the primary insulin-         | disease, atherosclerosis,              |   |
| responsive glucose transporter in fat | microvascular disease, hypertension,   |   |
| and muscle tissue. Exemplary assays   | stroke, and other diseases and         |   |
| that may be used or routinely         | disorders as described in the          |   |
| modified to test for DMEF1 response   | "Cardiovascular Disorders" section     |   |
| element activity (in adipocytes and   | below), dyslipidemia, endocrine        |   |
| pre-adipocytes) by polypeptides of    | disorders (as described in the         | _ |
| the invention (including antibodies   | "Endocrine Disorders" section          | _ |
| and agonists or antagonists of the    | below), neuropathy, vision             | _ |
| invention) include assays disclosed   | impairment (e.g., diabetic retinopathy |   |
| inThai, M.V., et al., J Biol Chem,    | and blindness), ulcers and impaired    | _ |
| 273(23):14285-92 (1998); Mora, S.,    | wound healing, and infection (e.g.,    | _ |
| et al., J Biol Chem, 275(21):16323-8  | infectious diseases and disorders as   |   |
| (2000); Liu, M.L., et al., J Biol     | described in the "Infectious           |   |
| Chem, 269(45):28514-21 (1994);        | Diseases" section below, especially    |   |
| "Identification of a 30-base pair     | of the urinary tract and skin). An     | _ |
| regulatory element and novel DNA      | additional highly preferred indication |   |
| binding protein that regulates the    | is obesity and/or complications        |   |
| human GLUT4 promoter in               | associated with obesity. Additional    |   |
| transgenic mice", J Biol Chem. 2000   | highly preferred indications include   |   |
| Aug 4;275(31);23666-73; Berger, et    | weight loss or alternatively, weight   | _ |
| al., Gene 66:1-10 (1988); and,        | gain. Additional highly preferred      | _ |
| Cullen, B., et al., Methods in        | indications are complications          |   |
| Enzymol. 216:362–368 (1992), the      | associated with insulin resistance.    | _ |
|                                       |                                        |   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | obesity and/or complications is obesity and/or complications obesity and/or complications obesity and/or complications is associated with obesity. Additional highly preferred indications include gain. An additional highly preferred indication is also additional highly preferred indication is as complication associated with fasteries mellins. An additional highly preferred indication is as complication associated with diabetic repimpality, Idiatedic relationship, Idiatedic relationship, and/or other diseases and disorders as secretion below, diabetic neuropathy, and/or other diseases and disorders as secrition below, diabetic neuropathy.  (e.g., due to diabetic neuropathy.                                                                                 |
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| contents of each of which is herein<br>incorporated by reference in its<br>entirey. Adipocytes and pare be used<br>according to these assays are publicly<br>according to these assays are publicly<br>available (e.g., Impagi the ATCCP)<br>and/or may be routinely generated.<br>Exemplar cells that may be used<br>according to these assays include the<br>according to the according to<br>according to the according to<br>according to the according to<br>according to the according to<br>according to the according to<br>the according to the according to the according to the according<br>to the according to the according to the according to the according<br>to the according to the according | transacription through the cAMP<br>transacription through the cAMP<br>transacription through the cAMP<br>the proposed element are well-known in<br>the art and may be used or routinely<br>the considered to assess the ability of<br>polypespides of the invention in<br>the polypespides of the invention in<br>polypespides of the invention in<br>function of the invention in<br>function of the properties of<br>the polypespides of the invention in<br>function of the properties of<br>the polypespides of the properties<br>the properties of<br>was supposed to identify is<br>that activate the cAMP signaling<br>that activate the cAMP signaling<br>adjougness, and is involved in<br>adjougness, and is involved in<br>adjougness, and is involved in<br>adjougness. (REF |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | transcription of<br>transcription through<br>the properties of<br>adipocytes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 376                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HYTN01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 172                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|     |         |     |                       | July daug - 1-3 - 11-1                   | 7                                      |
|-----|---------|-----|-----------------------|------------------------------------------|----------------------------------------|
|     |         |     |                       | uanscription factor CNLD (CNL            | diadelle nemopaniy or brood vesser     |
|     |         |     |                       | binding protein). Exemplary assays       | blockage), seizures, mental            |
|     |         |     |                       | for transcription through the cAMP       | confusion, drowsiness, nonketotic      |
|     |         |     |                       | response element that may be used or     | hyperglycemic-hyperosmolar coma,       |
|     |         |     |                       | routinely modified to test cAMP-         | cardiovascular disease (e.g., heart    |
|     |         |     |                       | response element activity of             | disease, atherosclerosis,              |
|     |         |     |                       | polypeptides of the invention            | microvascular disease, hypertension,   |
|     |         |     |                       | (including antibodies and agonists or    | stroke, and other diseases and         |
|     |         |     |                       | antagonists of the invention) include    | disorders as described in the          |
|     |         |     |                       | assays disclosed in Berger et al.,       | "Cardiovascular Disorders" section     |
|     |         |     |                       | Gene 66:1-10 (1998); Cullen and          | below), dyslipidemia, endocrine        |
|     |         |     |                       | Malm, Methods in Enzymol                 | disorders (as described in the         |
|     |         |     |                       | 216:362-368 (1992); Henthorn et al.,     | "Endocrine Disorders" section          |
|     |         |     |                       | Proc Natl Acad Sci USA 85:6342-          | below), neuropathy, vision             |
|     |         |     |                       | 6346 (1988); Reusch et al., Mol Cell     | impairment (e.g., diabetic retinopathy |
|     |         |     |                       | Biol 20(3):1008-1020 (2000); and         | and blindness), ulcers and impaired    |
|     |         |     |                       | Klemm et al., J Biol Chem 273:917-       | wound healing, and infection (e.g.,    |
|     |         |     |                       | 923 (1998), the contents of each of      | infectious diseases and disorders as   |
|     |         |     |                       | which are herein incorporated by         | described in the "Infectious           |
|     |         |     |                       | reference in its entirety. Pre-          | Diseases" section below, especially    |
|     |         |     |                       | adipocytes that may be used              | of the urinary tract and skin), carpal |
|     |         |     |                       | according to these assays are publicly   | tunnel syndrome and Dupuytren's        |
|     |         |     |                       | available (e.g., through the ATCCTM)     | contracture). Additional highly        |
|     |         |     |                       | and/or may be routinely generated.       | preferred indications are              |
|     |         |     |                       | Exemplary mouse adipocyte cells          | complications associated with insulin  |
|     |         |     |                       | that may be used according to these      | resistance.                            |
|     |         |     |                       | assays include 3T3-L1 cells. 3T3-L1      |                                        |
|     |         |     |                       | is an adherent mouse preadipocyte        |                                        |
|     |         |     |                       | cell line that is a continuous substrain |                                        |
|     |         |     |                       | of 3T3 fibroblast cells developed        |                                        |
|     |         |     |                       | through clonal isolation and undergo     |                                        |
|     |         |     |                       | a pre-adipocyte to adipose-like          |                                        |
|     |         |     |                       | conversion under appropriate             |                                        |
|     |         |     |                       | differentiation conditions known in      |                                        |
|     |         |     |                       | the art.                                 |                                        |
|     | HNTNI01 | 576 | Activation of         | Assays for the activation of             | A highly preferred indication is       |
| 172 |         |     | transcription through | transcription through the Serum          | obesity and/or complications           |
|     |         |     |                       |                                          |                                        |

| serum response element | Response Element (SRE) are well-         | associated with obesity. Additional    |
|------------------------|------------------------------------------|----------------------------------------|
| in the ambodies.       | routinely modified to assess the         | weight loss or alternatively, weight   |
|                        | ability of polypeptides of the           | gain. An additional highly preferred   |
|                        | invention (including antibodies and      | indication is diabetes mellitus. An    |
|                        | agonists or antagonists of the           | additional highly preferred indication |
|                        | invention) to regulate the serum         | is a complication associated with      |
|                        | response factors and modulate the        | diabetes (e.g., diabetic retinopathy,  |
|                        | expression of genes involved in          | diabetic nephropathy, kidney disease   |
|                        | growth. Exemplary assays for             | (e.g., renal failure, nephropathy      |
|                        | transcription through the SRE that       | and/or other diseases and disorders as |
|                        | may be used or routinely modified to     | described in the "Renal Disorders"     |
|                        | test SRE activity of the polypeptides    | section below), diabetic neuropathy,   |
|                        | of the invention (including antibodies   | nerve disease and nerve damage         |
|                        | and agonists or antagonists of the       | (e.g., due to diabetic neuropathy),    |
|                        | invention) include assays disclosed in   | blood vessel blockage, heart disease,  |
|                        | Berger et al., Gene 66:1-10 (1998);      | stroke, impotence (e.g., due to        |
|                        | Cullen and Malm, Methods in              | diabetic neuropathy or blood vessel    |
|                        | Enzymol 216:362-368 (1992);              | blockage), seizures, mental            |
|                        | Henthorn et al., Proc Natl Acad Sci      | confusion, drowsiness, nonketotic      |
|                        | USA 85:6342-6346 (1988); and             | hyperglycemic-hyperosmolar coma,       |
|                        | Black et al., Virus Genes 12(2):105-     | cardiovascular disease (e.g., heart    |
|                        | 117 (1997), the content of each of       | disease, atherosclerosis,              |
|                        | which are herein incorporated by         | microvascular disease, hypertension,   |
|                        | reference in its entirety. Pre-          | stroke, and other diseases and         |
|                        | adipocytes that may be used              | disorders as described in the          |
|                        | according to these assays are publicly   | "Cardiovascular Disorders" section     |
|                        | available (e.g., through the ATCCTM)     | below), dyslipidemia, endocrine        |
|                        | and/or may be routinely generated.       | disorders (as described in the         |
|                        | Exemplary mouse adipocyte cells          | "Endocrine Disorders" section          |
|                        | that may be used according to these      | below), neuropathy, vision             |
|                        | assays include 3T3-L1 cells. 3T3-L1      | impairment (e.g., diabetic retinopathy |
|                        | is an adherent mouse preadipocyte        | and blindness), ulcers and impaired    |
|                        | cell line that is a continuous substrain | wound healing, and infection (e.g.,    |
|                        | of 3T3 fibroblast cells developed        | infectious diseases and disorders as   |
|                        | through clonal isolation and undergo     | described in the "Infectious           |
|                        | a pre-adipocyte to adipose-like          | Diseases" section below). Additional   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                      | The Arter of Court of the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All and the All |
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| polypeptides of the invention of an against or an against so of an against so of the invention of an against so of the including authorities and against or an adaptate of include assistant of inmune cells include assistant in "Lota", I at human cosinophilic in "Lota", Lymphonni, Im. 7(3):24-36 (192); Buttadayan S. (Zomulooype Imacrophage colony-stimulating factor and interdeliaris activate STAT5 and induce CISI mRAA in human peripheral blood cosinophilis" And Respit Cell Mol Bod.  Mar. 24(3):312-6 (2001), and, Du J., et "Engagement of the Cell adupter in indefendent 5 signaling in cosmophilis 13 (67-75 (2001), and the cosmophilis 13 (67-75 (2001)), and the butter of colling of the cost of the adupter in indefendent 5 signaling in comportated by reference in its incorporated by reference in its incorporated by reference in its incorporated by reference in its month of the costophilis Eosiophilis are a type of immune cell important in the line stage of altergia creation. Increases in GAS mediated transcription in GAS mediated transcription in | cosmophils is typically a result of STAT activation, normally a direct consequence of interleukin or other cytokine receptor stimulation (e.g. II.3. IL.5 or GMCSF). | A more for the minimum of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                      | 4-40-40-6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                      | 263                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                      | TINTENTO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | _                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| _                                 | _                                  | _                                    | _                                      | _                                    | _                                     | _                                | _                                   | _                            | _                           | _                                  | _                                 | _                                    | _                                 | _                                   | _                                   | _                                  | _                                      | _                                   | _                           | _                           | _                                   | _                              | _                          | _                                  | _                                    | _                                | _                                     | _                                    | _                               | _                              | _                                    | _                                 | _                              | _                                     | _                                 | _                                 |
|-----------------------------------|------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|---------------------------------------|----------------------------------|-------------------------------------|------------------------------|-----------------------------|------------------------------------|-----------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-----------------------------|-----------------------------|-------------------------------------|--------------------------------|----------------------------|------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|--------------------------------------|---------------------------------|--------------------------------|--------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|-----------------------------------|-----------------------------------|
| asthma, allergy, hypersensitivity | reactions, and inflammation.       | Preferred indications include        | infection (e.g., an infectious disease | as described below under "Infectious | Disease"), immunological disorders,   | inflammation and inflammatory    | disorders (e.g., as described below | under "Immune Activity", and | "Blood-Related Disorders"). | Preferred indications include      | autoimmme diseases (e.g.,         | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below) and      | immunodeficiencies (e.g., as        | described below).                  |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |
| transcription through the NFKB    | response element are well-known in | the art and may be used or routinely | modified to assess the ability of      | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) to | regulate NFKB transcription factors | and modulate expression of   | immunomodulatory genes.     | Exemplary assays for transcription | through the NFKB response element | that may be used or rountinely       | modified to test NFKB-response    | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in | Enzymol 216:362-368 (1992); | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Valle | Blazquez et al, Immunology | 90(3):455-460 (1997); Aramburau et | al., J Exp Med 82(3):801-810 (1995); | and Fraser et al., 29(3):838-844 | (1999), the contents of each of which | are herein incorporated by reference | in its entirety. For example, a | reporter assay (which measures | increases in transcription inducible | from a NFkB responsive element in | EOL-1 cells) may link the NFKB | element to a repeorter gene and binds | to the NFKB transcription factor, | which is upregulated by cytokines |
| transcription through             | NFKB response                      | element in immune                    | cells (such as EOL1                    | cells).                              |                                       |                                  |                                     |                              |                             |                                    |                                   |                                      |                                   |                                     |                                     |                                    |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |
|                                   |                                    |                                      |                                        |                                      |                                       |                                  |                                     |                              |                             |                                    |                                   |                                      |                                   |                                     |                                     |                                    |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |
|                                   |                                    |                                      |                                        |                                      |                                       |                                  |                                     |                              |                             |                                    |                                   |                                      |                                   |                                     |                                     |                                    |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |
| 172                               |                                    |                                      |                                        |                                      |                                       |                                  |                                     |                              |                             |                                    |                                   |                                      |                                   |                                     |                                     |                                    |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | A highly preferred indication is diabetes mellius.  A highly preferred indication is a complication as a complication as sociated with diabetes (e.g., diabetes (e.g., diabetes regions).  A proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal process and disorders as described in the Rean Disorders as described in the Rean Disorders are disease and neve diamage (e.g. the office in the public proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal proposal prop |
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| and other factors. Exemplary mmme cells had may be used according to these assays include exceptibilists as the human E/O I cell line of cosinophilis, as the pluman ecolor important in the allergie responses; they are recurided to important in the allergie responses; they are recurided to responses; they are recurided to responses of the stage allergie response of the stage allergie response of the stage allergie response of the stage allergie response of the stage allergie response of the stage allergie response of the stage allergie response of the stage allergie | transcription of Maile Enzyme are well-known in the art and may be used or routinely modified to assess the art and may be used or routinely modified to assess the art and may be used or routinely modified to assess the art and may be used or routinely modified to assess the art and may be used to the art and may be used to the art and are are are art and are are are are are are are are are are                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | trenscription of Malic<br>Enzyme in adipocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 376                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HNTN01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 172                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                       | in: Streeper, R.S., et al., Mol<br>Endocrinol, 12(11):1778-91 (1998); | disorders (as described in the "Endocrine Disorders" section         |
|-----|---------|-----|-----------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------|
|     |         |     |                       | Garcia-Jimenez, C., et al., Moi<br>Endocrinol, 8(10):1361-9 (1994);   | nelow), neuropatny, vision<br>impairment (e.g., diabetic retinopathy |
|     |         |     |                       | Barroso, I., et al., J Biol Chem,                                     | and blindness), ulcers and impaired                                  |
|     |         |     |                       | 274(25):17997-8004 (1999);                                            | wound healing, and infection (e.g.,                                  |
|     |         |     |                       | lipenberg, A., et al., J Biol Chem,                                   | infectious diseases and disorders as                                 |
|     |         |     |                       | 272(32):20108-20117 (1997);                                           | described in the "Infectious                                         |
|     |         |     |                       | Berger, et al., Gene 66:1-10 (1988);                                  | Diseases" section below, especially                                  |
|     |         |     |                       | and, Cullen, B., et al., Methods in                                   | of the urinary tract and skin), carpal                               |
|     |         |     |                       | Enzymol. 216:362–368 (1992), the                                      | ne a                                                                 |
|     |         |     |                       | contents of each of which is herein                                   | contracture). An additional                                          |
|     |         |     |                       | incorporated by reference in its                                      | highly preferred indication is obesity                               |
|     |         |     |                       | entirety. Hepatocytes that may be                                     | and/or complications associated with                                 |
|     |         |     |                       | used according to these assays are                                    | obesity. Additional highly preferred                                 |
|     |         |     |                       | publicly available (e.g., through the                                 | indications include weight loss or                                   |
|     |         |     |                       | ATCCTM) and/or may be routinely                                       | alternatively, weight gain.                                          |
|     |         |     |                       | generated. Exemplary hepatocytes                                      | Aditional highly preferred                                           |
|     |         |     |                       | that may be used according to these                                   | indications are complications                                        |
|     |         |     |                       | assays includes the H4IIE rat liver                                   | associated with insulin resistance.                                  |
|     |         |     |                       | hepatoma cell line.                                                   |                                                                      |
|     | HNTNI01 | 576 | Activation of         | This reporter assay measures                                          | Highly preferred indications include                                 |
| 172 |         |     | transcription through | activation of the GATA-3 signaling                                    | allergy, asthma, and rhinitis.                                       |
|     |         |     | GATA-3 response       | pathway in HMC-1 human mast cell                                      | Additional preferred indications                                     |
|     |         |     | element in immune     | line. Activation of GATA-3 in mast                                    | include infection (e.g., an infectious                               |
|     |         |     | cells (such as mast   | cells has been linked to cytokine and                                 | disease as described below under                                     |
|     |         |     | cells).               | chemokine production. Assays for                                      | "Infectious Disease"), and                                           |
|     |         |     |                       | the activation of transcription                                       | inflammation and inflammatory                                        |
|     |         |     |                       | through the GATA3 response                                            | disorders. Preferred indications also                                |
|     |         |     |                       | element are well-known in the art                                     | include blood disorders (e.g., as                                    |
|     |         |     |                       | and may be used or routinely                                          | described below under "Immune                                        |
|     |         |     |                       | modified to assess the ability of                                     | Activity", "Blood-Related                                            |
|     |         |     |                       | polypeptides of the invention                                         | Disorders", and/or "Cardiovascular                                   |
|     |         |     |                       | (including antibodies and agonists or                                 | Disorders"). Preferred indications                                   |
|     |         |     |                       | antagonists of the invention) to                                      | include autoimmune diseases (e.g.,                                   |
|     |         |     |                       | regulate GATA3 transcription factors                                  | rheumatoid arthritis, systemic lupus                                 |
|     |         |     |                       | and modulate expression of mast cell                                  | erythematosis, multiple sclerosis                                    |

| allergy, asthma, and rhintis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease", and inflammation and inflammatory            | include broad disorders related interacts and include the old disorders (e.g., as excitable blook under "Immune Activity". Blood-Related Disorders, and or "Cardiovascular Disorders", and or "Cardiovascular Disorders", and or "Cardiovascular Disorders", and remained edisorses (e.g., include amontmune diseases (e.g., include amontmune diseases) (e.g., instemine application in the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the |
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| activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription | angugan to water a water to a Activated Techkova in the art and may be teacher at evel below in the art and may be used or routined, to seek or routined, to seek or routined, to seek or routined, to seek or routined, to oblight on the oblight of polypsphakes of the invention) to regular RNAT transaction to the transaction for the angular RNAT transaction to the part of the routined polyper disc of the invention. Exemplary assays for transaction of thought the NKAT response element that may be used or funding broading to the NKAT response element that may be used or funding broading to the NKAT response element and may be used or funding broading to the NKAT response element and may be used or funding broading to the NKAT response element and may be used or funding broading analysis and gonists or for the part of the invention (including unthodies and agonists or funding the language of the invention (including unthodies and agonists or funding the language of the including the part of the including the part of the including the part of the including the part of the including the part of the including the part of the including the part of the including the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of the part of |
| reasscription through NFAT response clement in immune cells (such as mast cells).                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 172                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| Burkiu's Jumphoma, arthritis, AIDS, agambomous itseese, in humanaoy bowd theseas, sepsis, neutropenia, prurupophia, prosis, superopenia, prategista, guesties, supression of mamure reactions to transplanted of mamure reactions to transplanted mamure reactions, to transplanted agas and tistas, bemophilla, hyperosagilation, diabetes mellins, cucho-aeditis, meningitis, and Lymx Disease.                                                                                                                                                                      | allegy, stellun, and rhintis, allegy, stellun, and rhintis, allegy, stellun, and rhintis, additional thighty preferred indications includes include to the control indications include include the control indications include include the control indications include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include include |
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| 188-527-537 (1998), the contents of cash of which we better intorporated by reference in its return. Mass cash the many of easily carriery. Mass cash that may be used according to these assays are publicly. ATCCVP, Exemplary human mass calls that may be used according to these assays include the Human mass cell that may be unterature human mass cell the cashished from the mast cell the cashished from the mast cell thekemia, and catholist many chancelers is a proposal part of the mass cell telekemia, and catholist many chancelers is a financiar. | activation of the NFBs signaling behavior of the NFBs signaling behavior in MRC. I annuar mast cell line. Activation of NFBs in must cell in a Activation of NFBs in must cell in the activation of the NFBs in must cell in the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the act |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Avariation of transcription through through of the response of the response cells, such as must cells,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 376                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HNTN00                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 221                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                                                                                          | and agonists or antigonists of the invention (including antibodies and agonists or antigonists of the including antibodies are supported to the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection of the collection o | Disorders'). Preferred indications Disorders'). Preferred indications Charles and cancer, such sas, fore exemple, leakemia, and prostate, lymphoma, melanoma, and prostate, lymphoma, melanoma, and prostate, somphigeal, sommel, brain, liver, esophageal, sommel, brain, liver, below, under "Hyperproliferative Disorders".                                                                                                                                                                                             |
|-----|---------|-----|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 172 | HNTNIOI | 576 | Activation of<br>transcription through<br>STAT6 response<br>element in immune<br>cells). | Assays for the activation of marketels.  Assays for the activation of manazing in the magnitude the Signal Transcription (STATO) response element in immune cells (each as in the human HMC-1 mast cell line) are used or routinely modified to assess the ability of poptyperidies of the invention (including antibodies and pages or anguines and magnitude).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Highly preferred indications include Additional lightly preferred Additional lightly preferred Additional lightly preferred included including cg, and infections cd, and including cd, and infections classes as describe thelow infections classes as described below infections classes as described below inductions bissess, and inflammation and inflammatory disorders. Preferred indications also immunological disorders (cg, as excelled below under "Immune Activity", "Shood-kelated Activity", "Shood-kelated |

|     |         |     |                       | transcription factors and modulate         | Disorders" and/or "Cardiogascular     |
|-----|---------|-----|-----------------------|--------------------------------------------|---------------------------------------|
|     |         |     |                       | the expression of multiple genes           | Disorders") autoimmine diseases       |
|     |         |     |                       | Exemplary assays for transcription         | (e.g., rheumatoid arthritis, systemic |
|     |         |     |                       | through the STAT6 response element         | lupus erythematosis, multiple         |
|     |         |     |                       | that may be used or routinely              | sclerosis and/or as described below), |
|     |         |     |                       | modified to test STAT6 response            | and immunodeficiencies (e.g., as      |
|     |         |     |                       | element activity of the polypeptides       | described below). Preferred           |
|     |         |     |                       | of the invention (including antibodies     | indications include neoplastic        |
|     |         |     |                       | and agonists or antagonists of the         | diseases (e.g., leukemia, lymphoma,   |
|     |         |     |                       | invention) include assays disclosed in     | melanoma, and/or as described below   |
|     |         |     |                       | Berger et al., Gene 66:1-10 (1998);        | under "Hyperproliferative             |
|     |         |     |                       | Cullen and Malm, Methods in                | Disorders"). Preferred indications    |
|     |         |     |                       | Enzymol 216:362-368 (1992);                | include neoplasms and cancer, such    |
|     |         |     |                       | Henthorn et al., Proc Natl Acad Sci        | as, for example, leukemia,            |
|     |         |     |                       | USA 85:6342-6346 (1988); Sherman,          | lymphoma, melanoma, and prostate,     |
|     |         |     |                       | Immunol Rev 179:48-56 (2001);              | breast, lung, colon, pancreatic,      |
|     |         |     |                       | Malaviya and Uckun, J Immunol              | esophageal, stomach, brain, liver and |
|     |         |     |                       | 168:421-426 (2002); Masuda et al., J       | urinary cancer. Other preferred       |
|     |         |     |                       | Biol Chem 275(38):29331-29337              | indications include benign            |
|     |         |     |                       | (2000); and Masuda et al., J Biol          | dysproliferative disorders and pre-   |
|     |         |     |                       | Chem 276:26107-26113 (2001), the           | neoplastic conditions, such as, for   |
|     |         |     |                       | contents of each of which are herein       | example, hyperplasia, metaplasia,     |
|     |         |     |                       | incorporated by reference in its           | and/or dysplasia. Preferred           |
|     |         |     |                       | entirety. Mast cells that may be used      | indications include hematopoietic     |
|     |         |     |                       | according to these assays are publicly     | and immunological disorders such as   |
|     |         |     |                       | available (e.g., through the               | arthritis, AIDS, granulomatous        |
|     |         |     |                       | ATCC <sup>TM</sup> ). Exemplary human mast | disease, inflammatory bowel disease,  |
|     |         |     |                       | cells that may be used according to        | sepsis, neutropenia, neutrophilia,    |
|     |         |     |                       | these assays include the HMC-1 cell        | psoriasis, suppression of immune      |
|     |         |     |                       | line, which is an immature human           | reactions to transplanted organs and  |
|     |         |     |                       | mast cell line established from the        | tissues, hemophilia,                  |
|     |         |     |                       | peripheral blood of a patient with         | hypercoagulation, diabetes mellitus,  |
|     |         |     |                       | mast cell leukemia, and exhibits           | endocarditis, meningitis, and Lyme    |
|     |         |     |                       | many characteristics of immature           | Discase.                              |
|     |         |     |                       | mast cells.                                |                                       |
|     | HNTN101 | 576 | Activation of         | This reporter assay measures               | Highly preferred indication includes  |
| 172 |         |     | transcription through | activation of the NFkB signaling           | allergy, asthma, and rhinitis.        |

| Additional highly preferred     | indications include infection (e.g., an | infectious disease as described below | under "Infectious Disease"), and   | inflammation and inflammatory        | disorders. Preferred indications  | include immunological and     | hempatopoietic disorders (e.g., as    | described below under "Immune    | Activity", and "Blood-Related       | Disorders"). Preferred indications | also include autoimmune diseases | (e.g., rheumatoid arthritis, systemic | lupus erythematosis, multiple     | sclerosis and/or as described below) | and immunodeficiencies (e.g., as | described below). Preferred         | indications also include neoplastic | diseases (e.g., leukemia, lymphoma, | melanoma, and/or as described below    | under "Hyperproliferative           | Disorders"). Preferred indications | include neoplasms and cancer, such | as, for example, leukemia,          | lymphoma, melanoma, and prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver,    | urinary tract cancers and as described | below under "Hyperproliferative  | Disorders".                          |                                        |                              |                                       |                                      |                                   |                                      |                                  |
|---------------------------------|-----------------------------------------|---------------------------------------|------------------------------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------|---------------------------------------|-----------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|------------------------------------|------------------------------------|-------------------------------------|-----------------------------------|----------------------------------|---------------------------------------|----------------------------------------|----------------------------------|--------------------------------------|----------------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|--------------------------------------|----------------------------------|
| nathway in Ku812 human basonhil | cell line. Assays for the activation of | transcription through the NFKB        | response element are well-known in | the art and may be used or routinely | modified to assess the ability of | polypeptides of the invention | (including antibodics and agonists or | antagonists of the invention) to | regulate NFKB transcription factors | and modulate expression of         | immunomodulatory genes.          | Exemplary assays for transcription    | through the NFKB response element | that may be used or rountinely       | modified to test NFKB-response   | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the  | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in        | Enzymol 216:362-368 (1992);        | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Marone   | et al, Int Arch Allergy Immunol  | 114(3):207-17 (1997), the contents of | each of which are herein               | incorporated by reference in its | entirety. Basophils that may be used | according to these assays are publicly | available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary human | basophil cell lines that may be used | according to these assays include | Ku812, originally established from a | patient with chronic myelogenous |
| NFKB response                   | element in immune                       | cells (such as                        | basophils).                        |                                      |                                   |                               |                                       |                                  |                                     |                                    |                                  |                                       |                                   |                                      |                                  |                                     |                                     |                                     |                                        |                                     |                                    |                                    |                                     |                                   |                                  |                                       |                                        |                                  |                                      |                                        |                              |                                       |                                      |                                   |                                      |                                  |
|                                 |                                         |                                       |                                    |                                      |                                   |                               |                                       |                                  |                                     |                                    |                                  |                                       |                                   |                                      |                                  |                                     |                                     |                                     |                                        |                                     |                                    |                                    |                                     |                                   |                                  |                                       |                                        |                                  |                                      |                                        |                              |                                       |                                      |                                   |                                      |                                  |

|                                                                                                                          | include blood disorders (e.g., ste<br>except be known under 'Inname<br>Activity," 'Blood-Related under 'Inname<br>Activity," 'Blood-Related under 'Inname<br>Disorders', and or 'Cordiovascular<br>Disorders', and or 'Cordiovascular<br>Infrastructural under 'Inname<br>Infrastructural under Inname of the Search<br>Infrastructural under Search (e.g., ste<br>systemic lupus cythermosis,<br>systemic lupus cythermosis,<br>systemic lupus cythermosis, and<br>below), immunde response, and<br>exact bed know, hossing at T cell-<br>mediated immune response, and<br>immune response, and exact bed known<br>prevered infeatous is infection (e.g., ste<br>infection diseases is described<br>helw under 'Infectious Diseases').<br>Perfered infeatous Bisease, and<br>experient diseases (e.g., leukernit,<br>prophorm, and cross the contraction include<br>helw under 'Hipperrol infeatous<br>helw under 'Hipperrol infeatous<br>helw under 'Hipperrol infeatous<br>include reophisms and eneces, such<br>lymphorm, and prostute breast, lung<br>sonned, hen il itse red mirray<br>sonned, been preferent infeatous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| leukemia. It is an immature<br>prebasophilic cell line that can be<br>induced to differentiate into mature<br>basophils. | transcription through the Nuclear<br>Resease for the activation for a foreign of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the |
|                                                                                                                          | Activation of Activation of Intrascription of Intrascription through NEAT response cells (such is natural killer cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Ĭ                                                                                                                        | 271                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| disorders and pre-neoplastic conditions, such as, for example, by perplastin, metaplastia, and or objections, and or objections, such as a size of the proposition. Performed indeations also include anemia, pancytopenia, the proposeria, the modeyenia, themolocytopenia, pancytopenia, pancytopinia, | include preferred includions include neoplastic diseases (e.g., leukernin, pupploma, and ora sekestribenin pupploma, and ora sekestribenin below under "Hyperprolificrative below under "Hyperprolificrative below under "Hyperprolificrative production include neoplasms and neuers, such as, for example teukernin, lymphoma, for example teukernin, lymphoma, for example feukernin, lymphoma, ledgiari symphoma, diseasel, melanoma, and prosatic, lymphoma, and prosatic, diseasel, melanoma, and prosatic, diseasel, melanoma, herain, liver and diseasel, melanoma, herain, liver and mindendors include benign indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing indications in the processing in the processing indications in the processing in the processing in the processing indicatio |
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| herein incorporated by reference in a seriety. We cled that may be used according to these assays are publicly available (e.g., through the ATCC <sup>19</sup> ). Exemplary human NK et al. (a.g., through the ATCC <sup>19</sup> ). Exemplary human NK et al. (b. 1914). Exemplary human NK et al. (b. 1914). The through the through the NK-T cell these assays include the NK-T cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | transcription through the cleaman<br>transcription through the cleaman<br>transcription through the cleaman<br>transcription through the cleaman<br>responses cleament are well-known in<br>responses cleament are well-known in<br>modified to assess the ability of<br>pohypeptides of the invention of<br>cleaming the properties of the invention to<br>pohypeptides of the invention) to<br>read an area of the invention in<br>the pohyperides of the invention in<br>and modaling gene expression<br>in modaling gene expression<br>in modaling gene expression<br>functions. Evenphary assays for<br>transcription through the CdAS<br>response cleament that may be used or<br>response cleament that may be used or<br>response cleament activity of<br>response cleament activity of<br>response cleament activity of<br>response cleament activity of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| indications include autoimmune<br>diseases (e.g., rheumatoid arthritis,<br>systemic lupus erythematosis,<br>multipla colonosis, and the accepted | mumple sciencist and/or as described<br>below), immunodeficiencies (e.g., as<br>described below), boosting a T cell- | suppressing a T cell-mediated immine response. Additional                                         | preferred indications include inflammatory                         | disorders. Highly preferred<br>indications include blood disorders   | (e.g., as described below under      | "Immune Activity", "Blood-Related<br>Disorders", and/or "Cardiovascular        | Disorders"), and infection (e.g., viral | infections, tuberculosis, infections | associated with chronic | granulomatosus disease and | malignant osteoporosis, and/or an | infectious disease as described below | under intectious Disease ). An<br>additional preferred indication is | idiopathic pulmonary fibrosis. | Preferred indications include anemia, | pancytopenia, leukopenia, | lymphocytic anemia (ALL). | plasmacytomas, multiple myeloma, | arthritis, AIDS, granulomatous | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, | psoriasis, suppression of immune | reactions to transplanted organs and | tissues, hemophilia, | hypercoagulation, diabetes mellitus, |
|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------|-------------------------|----------------------------|-----------------------------------|---------------------------------------|----------------------------------------------------------------------|--------------------------------|---------------------------------------|---------------------------|---------------------------|----------------------------------|--------------------------------|--------------------------------------|------------------------------------|----------------------------------|--------------------------------------|----------------------|--------------------------------------|
| antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm Mathode in Francial                | Mathri, Methods in Firsymol<br>216:362-368 (1992); Henthorn et al.,<br>Proc Natl Acad Sci USA 85:6342-               | 0340 (1966), Mathemetr et al.,<br>Blood 93(6):1980-1991 (1999); and<br>Henttinen et al. I Immunol | 155(10):4582-4587 (1995), the contents of each of which are herein | incorporated by reference in its<br>entirety Exemplary human T cells | such as the SUPT cell line, that may | be used according to these assays are<br>publicly available (e.g., through the | ATCCTM).                                |                                      |                         |                            |                                   |                                       |                                                                      |                                |                                       |                           |                           |                                  |                                |                                      |                                    |                                  |                                      |                      |                                      |
|                                                                                                                                                  |                                                                                                                      |                                                                                                   |                                                                    |                                                                      |                                      |                                                                                |                                         |                                      |                         |                            |                                   |                                       |                                                                      |                                |                                       |                           |                           |                                  |                                |                                      |                                    |                                  |                                      |                      | _                                    |
|                                                                                                                                                  |                                                                                                                      |                                                                                                   |                                                                    |                                                                      |                                      |                                                                                |                                         |                                      |                         |                            |                                   |                                       |                                                                      |                                |                                       |                           |                           |                                  |                                |                                      |                                    |                                  |                                      |                      |                                      |
|                                                                                                                                                  |                                                                                                                      |                                                                                                   |                                                                    |                                                                      |                                      |                                                                                |                                         |                                      |                         |                            |                                   |                                       |                                                                      |                                |                                       |                           |                           |                                  |                                |                                      |                                    |                                  |                                      |                      |                                      |

| endocarditis, meningitis, Lyme<br>Disease, and asthma and allergy. | A highly perfected enhodiment of the invention includes a mothod for increasing muscle cal survival An alacumist highly preferred and another of the invention includes a method for invention includes a method for deveraging muscle cell survival in A preferred muscle cell survival in A preferred muscle cell survival in A preferred muscle cell survival in A preferred muscle cell surfaction. In a specific embodiment of the invention includes a method for similating muscle cell politication. In a specific embodiment of the invention includes a method for inhibiting muscle cell politication is a specific embodiment of the A preferred embodiment of the A preferred embodiment of the A preferred embodiment of the Provincion includes a method for similating muscle cell politication is an specific embodiment of the invention includes a method for similating muscle cell differentiation is similated. An alternative highly preferred and includes a method for inhibiting embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications includes a method for inhibiting muscle cell differentiation is inhibited. Highly preferred indications inhibited specific embodiment, skeletal muscle coll differentiation is inhibited. Highly preferred indications inhibited and alternative highly preferred indications inhibited and selected inferentiation is inhibited. Section of the invention includes a method for inhibiting section. Preferred indications inhibited and selected inferentiation is inhibited.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                                                                    | compple an GSK-3 kinsen seasy, for exemple an GSK-3 kinsen seasy, from the complete and the complete and the complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and complete and |
|                                                                    | Activation of State and Mache Cell Pl States<br>Signalling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                    | 577                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                    | IINTSV18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                    | 173                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| iated   "Hyperproliferative Disorders"), | tion endocrine disorders (e.g., as      | described below under "Endocrine | Disorders"), neural disorders (e.g., as | described below under "Neural | Activity and Neurological | Diseases"), blood disorders (e.g., as | described below under "Immune | Activity", "Cardiovascular | Disorders", and/or "Blood-Related | Disorders"), immune disorders (e.g., | as described below under "Immune | Activity"), and infection (e.g., as | described below under "Infectious | Disease"). A highly preferred | indication is diabetes mellitus. | An additional highly preferred | indication is a complication | associated with diabetes (e.g., | diabetic retinopathy, diabetic | nephropathy, kidney disease (e.g., | renal failure, nephropathy and/or | other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage (e.g, | due to diabetic neuropathy), blood | vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, |
|------------------------------------------|-----------------------------------------|----------------------------------|-----------------------------------------|-------------------------------|---------------------------|---------------------------------------|-------------------------------|----------------------------|-----------------------------------|--------------------------------------|----------------------------------|-------------------------------------|-----------------------------------|-------------------------------|----------------------------------|--------------------------------|------------------------------|---------------------------------|--------------------------------|------------------------------------|-----------------------------------|---------------------------------|------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|---------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|
| multinucleated myotubes and striated     | fibers after culture in differentiation | media.                           |                                         |                               |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |                               |                                  |                                |                              |                                 |                                |                                    |                                   |                                 |                                    |                                      |                                      |                                    |                                 |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |
|                                          |                                         |                                  |                                         |                               |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |                               |                                  |                                |                              |                                 |                                |                                    |                                   |                                 |                                    |                                      |                                      |                                    |                                 |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |
|                                          |                                         |                                  |                                         |                               |                           |                                       |                               |                            |                                   |                                      |                                  |                                     |                                   |                               |                                  |                                |                              |                                 |                                |                                    |                                   |                                 |                                    |                                      |                                      |                                    |                                 |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |

| _ |  | disorders as described in the          |
|---|--|----------------------------------------|
|   |  | "Cardiovascular Disorders" section     |
|   |  | helow) dyslinidemia endocrine          |
|   |  | disorders (as described in the         |
|   |  | "Endomine Disordon" motion             |
|   |  | Elidocrine Disorders section           |
|   |  | below), neuropathy, vision             |
|   |  | impairment (e.g., diabetic retinopathy |
|   |  | and blindness), ulcers and impaired    |
|   |  | wound healing, infections (e.g.,       |
|   |  | infectious diseases and disorders as   |
|   |  | described in the "Infectious           |
|   |  | Diseases" section below, especially    |
|   |  | of the urinary tract and skin), carpal |
|   |  | tunnel syndrome and Dupuytren's        |
|   |  | contracture). An additional            |
|   |  | highly preferred indication is obesity |
|   |  | and/or complications associated with   |
|   |  | obesity. Additional highly preferred   |
|   |  | indications include weight loss or     |
|   |  | alternatively, weight gain.            |
|   |  | Additional highly preferred            |
|   |  | indications are complications          |
|   |  | associated with insulin resistance.    |
|   |  | Additional highly preferred            |
|   |  | indications are disorders of the       |
|   |  | musculoskeletal system including       |
|   |  | myopathies, muscular dystrophy,        |
|   |  | and/or as described herein.            |
|   |  | Additional highly preferred            |
|   |  | indications include: myopathy,         |
|   |  | atrophy, congestive heart failure,     |
|   |  | cachexia, myxomas, fibromas,           |
|   |  | congenital cardiovascular              |
|   |  | abnormalities, heart disease, cardiac  |
|   |  | arrest, heart valve disease, and       |
|   |  | vascular disease. Highly               |
|   |  | preferred indications include          |

| rhadomyour, and the concept such as the dependent and concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such as the concept such | A highly preferred embodiment of the invention includes a method from strainlaining aginocyte proliferation. An alternative highly preferred embodiment of the includible and adjusciple proliferation. An alternative proliferation. An alternative highly preferred embodiment of the invention includes a method for includes a method for inhibiting adjuscype differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting and alternative highly preferred embodiment of the invention includes a method for inhibiting includes a method for inhibiting and a method for inhibiting and a method for inhibiting and a method for inhibiting and a method for inhibiting and a method for inhibiting adjuscyced efferentiation. An alternative inhibiting the extreme modition of the invention includes a method for intervaluing adjocycles. It lightly preferred indications include endocrine indications include endocrine indications include endocrine indications include endocrine indications include endocrine indications include endocrine indications include endocrine indications include endocrine indications includes endocrine indications include endocrine indications includes a method for indications include endocrine indications includes and the properties indications includes and endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine indications includes endocrine in |
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| MH. Prog. Biogram, Mol. 17(3, 49,479-500 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adjroyte calls that may be used according to these assests are publicly analysis of the seasy are publicly and the care assesting to the seasy are publicly on these assests are according to these assets are according to these assets are publicly on these assets include 717-Lt cells. 372-Lt is sun addrect mouse edite occleded in the flux may be used according to these assets include 373-Lt is sun addrect mouse edite developed through clonal isolation and underged are developed through clonal isolation and underged conversion under appropriate differentiation conditions known in the art. | MIII. Frog Biophys Mod Dis- Astro-500 (1999), the com- each of which are brettin incorporated by reference if entirety. Mouse adjacyster must be used according to it assays are publicly available through the ATC(229). Est mouses adjacyster or the content of these ass include 3T-4L cells. 3T-3L addressure mouse preadlacyst in flow or the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cell of the cel | bl 71(3- Highly preferred indications also rents of include neoplastic diseases (e.g., linomas, linosarcomas, and/or as |                                                                          | nese rreferred indications include blood (e.g., disorders (e.g., hypertension, congestive heart failure, blood vessel |                                                                  |                                                                    | ostrain of "Blood-Related Disorders"), immune bed disorders (e.g., as described below |                                      |                              |          | under "Infectious Disease").  A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a<br>complication associated with | diabetes (e.g., diabetic retinopathy, | Ge or renal failure menhronathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy) | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel | blockage), seizures, mental |
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| hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly | preferred indications are | ons ass | resistance. Additional highly | preferred indications are disorders of | the musculoskeletal systems | including myopathies, muscular | dystrophy, and/or as described | herein. Additional highly | preferred indications include, | hypertension, coronary artery | disease, dyslipidemia, gallstones, | osteoarthritis, degenerative arthritis, |
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| neoplasms and cancers, such as, for | example, leukemia, lymphoma,         | melanoma, and prostate, breast, lung, | colon, pancreatic, esophageal,  | stomach, brain, liver and urinary   | cancer. Other preferred indications | include benign dysproliferative | disorders and pre-neoplastic    | conditions, such as, for example, | hyperplasia, metaplasia, and/or | dysplasia. Preferred indications    | include blood disorders (e.g., as  | described below under "Immune        | Activity", "Blood-Related         | _                                     | Disorders"). Preferred indications | include autoimmme diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis   | and/or as described below) and   | immunodeficiencies (e.g., as       | described below). Preferred         | indications include anemia,        | pancytopenia, leukopenia,      | thrombocytopenia, Hodgkin's       | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple | myeloma, Burkitt's lymphoma,         | arthritis, AIDS, granulomatous    | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia,  | psoriasis, suppression of immune | reactions to transplanted organs and | tissues, hemophilia, | hypercoagulation, diabetes mellitus, | ÷. | Disease. An additional preferred |
| macrophages and mast cells. Such    | assays that may be used or routinely | modified to test immunomodulatory     | activity of polypeptides of the | invention (including antibodies and | agonists or antagonists of the      | invention) include the assays   | disclosed in Miraglia et al., J | Biomolecular Screening 4:193-204  | (1999); Rowland et al.,         | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000); Gonzalez | et al., J Clin Lab Anal 8(5):277-283 | (1194); Yssel et al., Res Immunol | 144(8):610-616 (1993); Bagley et al., | Nat Immunol 1(3):257-261 (2000);   | and van der Graaff et al.,        | Rheumatology (Oxford) 38(3):214-     | 220 (1999), the contents of each of | which are herein incorporated by | reference in its entirety. Human T | cells that may be used according to | these assays may be isolated using | techniques disclosed herein or | otherwise known in the art. Human | T cells are primary human         | lymphocytes that mature in the | thymus and express a T cell receptor | and CD3, CD4, or CD8. These cells | mediate humoral or cell-mediated     | immunity and may be preactivated to | enhance responsiveness to        | immunomodulatory factors.            |                      |                                      |    |                                  |
|                                     |                                      |                                       |                                 |                                     |                                     |                                 |                                 |                                   |                                 |                                     |                                    |                                      |                                   |                                       |                                    |                                   |                                      |                                     |                                  |                                    |                                     |                                    |                                |                                   |                                   |                                |                                      |                                   |                                      |                                     |                                  |                                      |                      |                                      |    |                                  |
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| indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                                                                      | Assays for the regulation of measuring the theory of the measuring of the measuring of measuring the Helbown in the at and may be used or countey modified to assess the ability of prohibition of the measuring of the invention to modified to assess the ability of or official magninists of the invention to activate the FAS promoter element in experter constraints and to regulate transcription of FAS, a key enzyme regulated by many transcription of PAS, a key enzyme regulated by many transcription of the proper including SREBP. Institution of the proper including SREBP institution increases FAS genter transcription in shown of diabetic mice. This strenglation of transcription in diagnosis of a part of the proper increase in diabetic mice and agonties or attagenesis of the measured in (the diagnosis or attagenesis of the act al., Binchem, 13 17 (Pt. 1):257–458. (1998): and, Cullen, B., et al., Gene 66-110 (1988): and, Cull |
|                                                                                                      | Regulation of transcription thrugh transcription thrugh transcription thrugh the RAS promoter element in hepatocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|                                                                                                      | HODDF13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| HODDF13 | 673 | hibibiion of squalene<br>synthetise gene<br>transcription.                                    | 1 2 4 4 5 6 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | turned syndrome and Dappytters's trained syndrome and Dappytters's contracture.  An additional ministration of additional and proferred indication is obesity and/or complications associated with indications include weight perferred indications include weight gain.  Additional highly preferred indications are complications are complications associated with installin resistance, associated with installin resistance. |
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| 0,      | 579 | Activation of CATA-3 response (GATA-3 response Celenent in immune cells (such as mast cells). | acardinate hepatocellular caretinoma cell line (ATCCP HB-<br>209-397) See Knowles et al., Science,<br>209-3979 (1980), the contents of<br>which are herein incorporated by<br>reference in its entirely.<br>This reporter assay measures<br>the service of the (ACM-A3 signaling<br>pathway in HMC-1 human mast cell<br>pathway in HMC-1 human mast cell<br>pathway in HMC-1 human mast cell<br>cells has been linked to cytokine and<br>cells has compared to cytokine and<br>compared to cytokine and<br>cells has compared to cytokine and<br>cells has compared to cytokine and<br>cells has compared to cytokine and<br>cells has cytokine and<br>cells has cytokine and<br>cells has cytokine and<br>cells has cytokine and<br>cells has cytokine and<br>cells has cytokine and<br>cells has cytokine and<br>cells has cytok | Highly preferred indications include allergy, staffing, and righnils. Additional preferred indications include infection (e.g., an infectional disease as described below under "Infections Dessease"), and inflammatory disease, Preferred indications also diseases.                                                                                                                                                            |

| described below under "Immine | Activity", "Blood-Related         | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications    | include autoimmune diseases (e.g., | s   rheumatoid arthritis, systemic lupus | 1 erythematosis, multiple sclerosis  | c and/or as described below) and    | immunodeficiencies (e.g., as      | described below). Preferred     | τ   indications include neoplastic   | discases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | _                             | r stomach, brain, liver, and urinary  | _                                     | below under "Hyperproliferative    | Disorders"). Other preferred    | _                        | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | _                                  | Hodgkin's disease, acute            | _                                   | _                                    | Burkitt's lymphoma, arthritis, AIDS, |                                  |                                       | <ul> <li>neutrophilia, psoriasis, suppression</li> </ul> | of immune reactions to transplanted | organs and tissues, hemophilia,            | hypercoagulation, diabetes mellitus, | endocarditis, meningitis, and Lyme  |
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| and may be used or martinely  | modified to assess the ability of | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to   | regulate GATA3 transcription factors     | and modulate expression of mast cell | genes important for immune response | development. Exemplary assays for | transcription through the GATA3 | response element that may be used or | routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its | entirety. Mast cells that may be used | according to these assays are publicly                   | available (e.g., through the        | ATCC <sup>TM</sup> ). Exemplary human mast | cells that may be used according to  | these assays include the HMC-1 cell |
|                               |                                   |                                    |                                       |                                    |                                          |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                               |                                       |                                       |                                    |                                 |                          |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                  |                                       |                                                          |                                     |                                            |                                      |                                     |
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| Discase.                                                                                                                                                                              | allegy, saftum, and rhintis, additional processor, and rhintis, additional professor infections include infections (e.g., an infections faction (e.g., an infections faction) (e.g., an infections) (e.g., an infections) (e.g., an information beauty), and influentation and influentation also influentation and influentation and influentation disorders. Preferred infections also include blood disorders, Perferred infections also include blood disorders, (e.g., as excepted below) under "Immune Artivity", "Hoto-de Raland Disorders," and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", and "Outsches", "Outsches", "Outsches "Outsches", "Outsche preferred indexions include benigm rad observed on years and pre- tract cancers and/or as described benigment of species and pre- described benigment of governed in the preferred objective and pre- described benigment of governed in preferred objective and pre- described benigment of governed and pre- proposities conditions, such as a for example "Disorders"). Other preferred as representations in metanlesia metanlesia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| line, which is an immature human mast cell inte established from the peripheral blood of a patient with mast cell tenkemia, and exhibits many characteristics of immature mast cells. | activation of the NPAT signaling plants and the NPAT signaling plants and the NPAT signaling plants of the NPAT signaling plants of the NPAT signaling plants of the NPAT signaling plants of the NPAT signaling plants of the NPAT signaling plants of the activation of transcription through the Nuclear Foxor of Actioned Feels of transcription from the well-known in the art and may be used or routinely of polyperpixels of the invention of the neighbour plants of the NPAT signaline NPAT transcription fronts and modaline expression of genes and modaline expressi |
|                                                                                                                                                                                       | Agrication of<br>transcription through<br>the Transparent<br>oler Transparent<br>cells (such its mast<br>cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                                                                                                                                                                       | HODDF13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                       | 175                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| and or dogslassi. Preferred indication of dogslassing and another parameters, paraviverant, leukenins, paraviverant, leukenins, leukenins, leukenins, leukenins, leukenins, leukenins, leukenins, mittile, myelens, palasmeyotums, mittile, myelens, plasmeyotums, mittile, myelens, plasmeyotums, mittile, myelens, granulorations disease, inflammatory famili, sporiissi, supression of cimmure reactions to transplanted organs and issues, kenopoliita, meturophiita, sporiissi, supression organismosticus, diseetes militus, endecentriis, memingiis, and Lyme Disease.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | light preferred indications include inflammation (caute and cironic).  Indiging the control of the caute of the caute and caute and allergy. Highly preferred indications allergy. Highly preferred indications inflammatory disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, neoplastic disorders, negativity—18 lood-Related Artivity—18 lood-Related Disorders, "High preferred Disorders" and or "Cardiovascular Disorders" and or "Cardiovascular disorders in circle neoplastic and disorders in circle neoplastic and disorders in circle neoplastic and disorders in circle neoplastic and disorders in circle neoplastic and disorders in circle neoplastic and disorders in circle neoplastic and disorders in circle neoplastic and disorders and disorders in circle neoplastic and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and disorders and display preferred disorders and display and display disorders and display and display disorders and display display disorders and display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display display di |
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| Bisothern Cell Biol 3 (10) 121 121 121 6 (1999), Ale al. J. Immunol (1999), Ale al. J. Immunol (1999), Ale al. J. Immunol (1999), Ale al. J. Immunol (1999), Ale al. J. Immunol (1999), Ale al. J. Immunol (1999), Ale al. J. Immunol (1994), Ale al. J. Immunol (1994), Incomens of the al. J. Exp Med Turner et al. J. Exp Med Turner et al. J. Exp Med Turner et al. J. Exp Med and Turner et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J. Exp Med et al. J | Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypendes of mercuinof including ambodies and aganists or antiganists of the invention (not regulate VCAM invention) to regulate VCAM or aganism or accomplete VCAM or and the proposition. For example, PMA/I may be used to meature the CAM or appealation of cell surface VCAM or and the proposition of the large are cells that line objects said on a modified and in the blood vessels, and are involved in function that include, but are not limited to.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| centeers such as, for example, the default, hypothera, relation, and more and cell carcinoma, and pressure, and resease, lung, color, pameratic, esophageal, stomach, brain, ifor and unionry cancer. Other preferred unionry cancer. Other preferred dyspontificative disorder, brain five and chapter of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of t |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| permeability, vascular tone, and manner cell extravastion. Exemplary endobtelial cells that may be used according to these assays include lumma umbitient vein a variable from commercial sources. The expression of VCAM (2016b), a memberne-associated protein, can be tupergallated by colorisms or other friends, and courtibutes to the extravassion of bymphospites, leucocytes and other manner cells from those vessels; thus VCAM expression plays a color immune cells from those vessels; thus VCAM expression plays as the world of the contraction of bymphospites, leucocytes and other manner cells from those vessels; thus VCAM expression plays as to inflammation repression plays as the inflammation repression plays as the inflammation repression plays as the inflammation responses.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | are swell-known in the art and may be well-known in the art and may be and motivated and routinely modified to assess ability of polypeptides of the invention to inhibit or activate of such an assay follows; Cells were pretreated as the MSD supermains or controls for 15-18 hours. SIAA eacivity was massive and the supermeated and explinely also may be a supplied to hour SIAA and of the supplied to hour SIAA and and epithelial colon adenocations are epithelial colon adenocations are epithelial colon adenocations are epithelial colon adenocations of particular supplied for studies on the mechanism of for studies on the mechanism of for studies on the mechanism of supplied and supplied to the contents of the supplied of the contents of which are remain incorporated by reference in its entirety. |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 579                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| A highly preferred embodiment of strain the invention infectors a method for strainlanding (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the meretian includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the simulation or independent of the indication is the simulation or indication is the simulation or indication is the simulation or indication is the simulation or indication is the simulation or indication in the indication is the simulation or indication in the indication is the simulation or indication of g.g. as described below under "Thambac Astriby." "Cardiovescular Discotters", and/or infection (e.g., as described below mader "Theories Discotters") and infective (e.g., as described below mader "Indications include Spisses"). Highly preferred indications include and a mediations include a mediation include and a mediations include a mediations include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation include a mediation and mediation include a mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and mediation and m | the distinguishment of seases (e.g., rheumand) arthritis, systemic lupus experanasis, multiple selerosis and/or as described below) and mammodeficiencies (e.g., as described below). Highly preferred administration of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the propert |
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| II6 FMAT. II6 is produced by T<br>cells and has somege effects on B<br>cells. II6 puricipates in II1<br>direct elig production and increases<br>light production (16x plays a robe in<br>moseal immanie). II6 induces<br>cyotoxic T cells. Dereguland<br>produces, and chronic maniera of<br>suppreproliferative diseases, plasmacyomis,<br>hyperproliferative diseases. Assays<br>the frammonopulation yand<br>differentiation fiscus proteins<br>produced by a large variety of cells<br>when the expression (et lis strongly<br>regulated by cyotikines, growth<br>feders, and may be used of<br>known in the str and may be used or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | continuely modified to assess the ability of polypeptides of the ability of polypeptides of the ability of polypeptides of the against or antagonists of the immunomodulation and modified the immunomodulation and finetion and modified real polyperapides of polypeptides of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the authority of and differentiation activity of any office and appendix of the anivolation (modifuling appendix of the anivolation activity of appendix of the anivolation activity of appendix of the anivolation (modifuling agonists or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Preduction of IL-6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 880                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HODDN92                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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| Highly preferred indications include a propositions and cancers, such as, mychotom, chipstoney/tom, lowering, mychotom, plasmacy/tom, om/tom/tom/tom/tom/tom/tom/tom/tom                                                                                                                                                                                                                                                                                                                                                                                                                                                               | A highly preterred embodiment of<br>the invention includes a method for<br>stimulating (e.g., increasing) MCP-1<br>production. An alternative highly<br>preterred embodiment of the<br>invention includes a method for<br>inhibiting (e.g., reducing) MCP-1 |
| assays disclosed in Mringlia et al., 204(1994). Behanderland Revening 4:193-204(1994). Behanderland Revening 4:193-204(1994). Rowhand et al., 204(1994). Rowhand et al., 204(1994). Rowhand et al., Chapheyer 6:138-160 (2000), and Mrehaselet al., 1 Immunol mol 185-2919-2926 (1997), the contents of each of which are breen in entirety. Human dehaltite cells hat may be used according to these assays runy be isolated using entirety. Human dehaltite cells hat when be used according to these assays runy be isolated using entirety. Human dehaltite cells hat otherwise Rowam in the art. Human otherwise Rowam in the art. Human otherwise Rowam in the art. Human coherwise Rowam in the art. Human enterpression culture, which, cells in asspension culture, which, cells in asspension culture, which, cell positification and functional activities. | MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotavis and activation of monocytes and Teels are well known in the art and may be used or routinely modified to assess                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Production of MCP-1                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 280                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HODDN92                                                                                                                                                                                                                                                     |
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| production. A highly preferred     | infectious disease as described below | under "Infectious Disease"). | Additional highly preferred | indications include inflammation and | inflammatory disorders. Preferred | indications include blood disorders | (e.g., as described below under     | "Immune Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"). Highly preferred | indications include autoimmune     | diseases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,     | multiple sclerosis and/or as described | below) and immunodeficiencies (e.g., | as described below). Preferred        | indications also include anemia,      | pancytopenia, leukopenia,              | thrombocytopenia, Hodgkin's   | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple      | myeloma, Burkitt's lymphoma, | arthritis, AIDS, granulomatous  | disease, inflammatory bowel disease, | sepsis, neutropenia, neutrophilia, | psoriasis, suppression of immune   | reactions to transplanted organs and | tissues, hemophilia,             | hypercoagulation, diabetes mellitus, | endocarditis, meningitis (bacterial | and viral), Lyme Disease, asthma, | and allergy Preferred indications | also include neoplastic diseases (e.g., | leukemia, lymphoma, and/or as          | described below under               |
| the ability of polypeptides of the | agonists or antagonists of the        | invention) to mediate        | immunomodulation, induce    | chemotaxis, and modulate immune      | cell activation. Exemplary assays | that test for immunomodulatory      | proteins evaluate the production of | cell surface markers, such as     | monocyte chemoattractant protein   | (MCP), and the activation of  | monocytes and T cells. Such assays | that may be used or routinely         | modified to test immunomodulatory | and diffferentiation activity of       | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Miraglia et al., J | Biomolecular Screening 4:193- | 204(1999); Rowland et al.,        | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000);    | Satthaporn and Eremin, J R Coll | Surg Ednb 45(1):9-19 (2001); and     | Verhasselt et al., J Immunol       | 158:2919-2925 (1997), the contents | of each of which are herein          | incorporated by reference in its | entirety. Human dendritic cells that | may be used according to these      | assays may be isolated using      | techniques disclosed herein or    | otherwise known in the art. Human       | dendritic cells are antigen presenting | cells in suspension culture, which, |
|                                    |                                       |                              |                             |                                      |                                   |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   |                                        |                                      |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 |                                      |                                    |                                    |                                      |                                  |                                      |                                     |                                   |                                   |                                         |                                        |                                     |
|                                    |                                       |                              |                             |                                      |                                   |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   |                                        |                                      |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 |                                      |                                    |                                    |                                      |                                  |                                      |                                     |                                   |                                   |                                         |                                        |                                     |
|                                    |                                       |                              |                             |                                      |                                   |                                     |                                     |                                   |                                    |                               |                                    |                                       |                                   |                                        |                                      |                                       |                                       |                                        |                               |                                   |                                     |                              |                                 |                                      |                                    |                                    |                                      |                                  |                                      |                                     |                                   |                                   |                                         |                                        |                                     |

| "Hyperprolliferative Disorders").  High preferred indications include neopleaens and cancers, such as, ferred including the conference, such as, ferred in the colon, panceratic, breast, lung, colon, panceratic, breast, lung, colon, panceratic, breast, lung, colon, panceratic, brain, liver, and uninary cancer. Other preferred indications include bening in conference indications include bening in conglishic conditions, such as, for neopleastic conditions, such as, for example, hyporphisai, metaphissia, and or dysplasia. | A highly preferred emboliment of the invention includes a method of a simulating MID 18 production. An alternative highly preferred includes a method for including of a method for including (e.g., stephenson, production, and a method for including (e.g., stephenson, production, production, and including of a microrion (e.g., an infection disease as described below under "Infections Bissase"). Preferred indications include blood discovers (e.g., as a described below under "Immune Arthry"). Bloodorfer (e.g., as described below under "Immune Arthry"). Bloodorfers (e.g., as described below under "Immune Diseases). Amotor "Cardiovascult" Diseases (e.g., Immune and Train and Or "Cardiovascult" Diseases (e.g., Immunodio affairies), systemic hipse expleminosis, mintiple schensos and or se described below) and immunodio-diseases (e.g., Immunodio affairies) include highly preferred indications include highly preferred indications include highly preferred indications include inflammation and immunosory diseaseds.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| when activated by antigen and/or volvenes, minine and upregulate T cell proliferation and functional activities.                                                                                                                                                                                                                                                                                                                                                                                                                            | immanomodulatory proteins of immanomodulatory proteins of the moduced by activated dendritic cells that upregalate of moduced by activated dendritic cells that upregalate or continely modulated to the continely of the polyperides of the investion polyperides of the investion polyperides of the investion polyperides and along is an appearance of the investion of the investion of the investion to modulate of the investion to modulate of the investion to modulate of the investion to modulate of the investion to modulate of the investion to modulate of the investion to the investion to modulate of the investion to the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of the investigation of |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Production of<br>MIP lapha                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 580                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HODDN92                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|     |         |     |                        | of the appropriate of the               | olinoinolisto anomoin apropriatorio     |
|-----|---------|-----|------------------------|-----------------------------------------|-----------------------------------------|
|     |         |     |                        | agomets or antagomets of the            | also include alicilità, paricy operità, |
|     |         |     |                        | invention) include assays disclosed in  | leukopenia, thrombocytopenia,           |
|     |         |     |                        | Miraglia et al., J Biomolecular         | Hodgkin's disease, acute                |
|     |         |     |                        | Screening 4:193-204(1999);              | lymphocytic anemia (ALL),               |
|     |         |     |                        | Rowland et al., "Lymphocytes: a         | plasmacytomas, multiple myeloma,        |
|     |         |     |                        | practical approach" Chapter 6:138-      | Burkitt's lymphoma, arthritis, AIDS,    |
|     |         |     |                        | 160 (2000); Satthaporn and Eremin, J    | granulomatous disease, inflammatory     |
|     |         |     |                        | R Coll Surg Ednb 45(1):9-19 (2001);     | bowel disease, sepsis, neutropenia,     |
|     |         |     |                        | Drakes et al., Transp Immunol           | neutrophilia, psoriasis, suppression    |
|     |         |     |                        | 8(1):17-29 (2000); Verhasselt et al., J | of immune reactions to transplanted     |
|     |         |     |                        | Immunol 158:2919-2925 (1997); and       | organs and tissues, hemophilia,         |
|     |         |     |                        | Nardelli et al., J Leukoc Biol 65:822-  | hypercoagulation, diabetes mellitus,    |
|     |         |     |                        | 828 (1999), the contents of each of     | endocarditis, meningitis, Lyme          |
|     |         |     |                        | which are herein incorporated by        | Disease, asthma, and allergy.           |
|     |         |     |                        | reference in its entirety. Human        | Preferred indications also include      |
|     |         |     |                        | dendritic cells that may be used        | neoplastic diseases (e.g., leukemia,    |
|     |         |     |                        | according to these assays may be        | lymphoma, and/or as described           |
|     |         |     |                        | isolated using techniques disclosed     | below under "Hyperproliferative         |
|     |         |     |                        | herein or otherwise known in the art.   | Disorders"). Highly preferred           |
|     |         |     |                        | Human dendritic cells are antigen       | indications include neoplasms and       |
|     |         |     |                        | presenting cells in suspension          | cancers, such as, leukemia,             |
|     |         |     |                        | culture, which, when activated by       | lymphoma, prostate, breast, lung,       |
|     |         |     |                        | antigen and/or cytokines, initiate and  | colon, pancreatic, esophageal,          |
|     |         |     |                        | upregulate T cell proliferation and     | stomach, brain, liver, and urinary      |
|     |         |     |                        | functional activities.                  | cancer. Other preferred indications     |
|     |         |     |                        |                                         | include benign dysproliferative         |
|     |         |     |                        |                                         | disorders and pre-neoplastic            |
|     |         |     |                        |                                         | conditions, such as, for example,       |
|     |         |     |                        |                                         | hyperplasia, metaplasia, and/or         |
|     |         |     |                        |                                         | dysplasia.                              |
|     | HODDN92 | 280 | Regulation of          | Assays for the regulation of            | A highly preferred indication is        |
| 176 |         |     | transcription through  | transcription through the FAS           | diabetes mellitus. An                   |
|     |         |     | the FAS promoter       | promoter element are well-known in      | additional highly preferred indication  |
|     |         |     | element in hepatocytes | the art and may be used or routinely    | is a complication associated with       |
|     |         |     |                        | modified to assess the ability of       | diabetes (e.g., diabetic retinopathy,   |
|     |         |     |                        | polypeptides of the invention           | diabetic nephropathy, kidney disease    |
|     |         |     |                        | (including antibodies and agonists or   | (e.g., renal failure, nephropathy       |

|  | antagonists of the invention) to               | and/or other diseases and disorders as |
|--|------------------------------------------------|----------------------------------------|
|  | activate the FAS promoter element in           | described in the "Renal Disorders"     |
|  | a reporter construct and to regulate           | section below), diabetic neuropathy,   |
|  | transcription of FAS, a key enzyme             | nerve disease and nerve damage         |
|  | for lipogenesis. FAS promoter is               | (e.g., due to diabetic neuropathy),    |
|  | regulated by many transcription                | blood vessel blockage, heart disease,  |
|  | factors including SREBP. Insulin               | stroke, impotence (e.g., due to        |
|  | increases FAS gene transcription in            | diabetic neuropathy or blood vessel    |
|  | livers of diabetic mice. This                  | blockage), seizures, mental            |
|  | stimulation of transcription is also           | confusion, drowsiness, nonketotic      |
|  | somewhat glucose dependent.                    | hyperglycemic-hyperosmolar coma,       |
|  | Exemplary assays that may be used              | cardiovascular disease (e.g., heart    |
|  | or routinely modified to test for FAS          | disease, atherosclerosis,              |
|  | promoter element activity (in                  | microvascular disease, hypertension,   |
|  | hepatocytes) by polypeptides of the            | stroke, and other diseases and         |
|  | invention (including antibodies and            | disorders as described in the          |
|  | agonists or antagonists of the                 | "Cardiovascular Disorders" section     |
|  | invention) include assays disclosed in         | below), dyslipidemia, endocrine        |
|  | Xiong, S., et al., Proc Natl Acad Sci          | disorders (as described in the         |
|  | U.S.A., 97(8):3948-53 (2000);                  | "Endocrine Disorders" section          |
|  | Roder, K., et al., Eur J Biochem,              | below), neuropathy, vision             |
|  | 260(3):743-51 (1999); Oskouian B,              | impairment (e.g., diabetic retinopathy |
|  | et al., Biochem J, 317 ( Pt 1):257-65          | and blindness), ulcers and impaired    |
|  | (1996); Berger, et al., Gene 66:1-10           | wound healing, and infection (e.g.,    |
|  | (1988); and, Cullen, B., et al.,               | infectious diseases and disorders as   |
|  | Methods in Enzymol. 216:362-368                | described in the "Infectious           |
|  | (1992), the contents of each of which          | Diseases" section below, especially    |
|  | is herein incorporated by reference in         | of the urinary tract and skin), carpal |
|  | its entirety. Hepatocytes that may be          | tunnel syndrome and Dupuytren's        |
|  | used according to these assays, such           | contracture). An additional            |
|  | as H4IIE cells, are publicly available         | highly preferred indication is obesity |
|  | (e.g., through the ATCC <sup>TM</sup> ) and/or | and/or complications associated with   |
|  | may be routinely generated.                    | obesity. Additional highly preferred   |
|  | Exemplary hepatocytes that may be              | indications include weight loss or     |
|  | used according to these assays                 | alternatively, weight gain.            |
|  | include rat liver hepatoma cell line(s)        | Aditional highly preferred             |
|  | inducible with glucocorticoids,                | indications are complications          |

|     |         |     |                       | insulin, or cAMP derivatives.         | associated with insulin resistance.    |
|-----|---------|-----|-----------------------|---------------------------------------|----------------------------------------|
|     | HODDN92 | 580 | Activation of         | This reporter assay measures          | Highly preferred indications include   |
| 176 |         |     | transcription through | activation of the GATA-3 signaling    | allergy, asthma, and rhinitis.         |
|     |         |     | GATA-3 response       | pathway in HMC-1 human mast cell      | Additional preferred indications       |
|     |         |     | element in immune     | line. Activation of GATA-3 in mast    | include infection (e.g., an infectious |
|     |         |     | cells (such as mast   | cells has been linked to cytokine and | discase as described below under       |
|     |         |     | cells).               | chemokine production. Assays for      | "Infectious Disease"), and             |
|     |         |     |                       | the activation of transcription       | inflammation and inflammatory          |
|     |         |     |                       | through the GATA3 response            | disorders. Preferred indications also  |
|     |         |     |                       | element are well-known in the art     | include blood disorders (e.g., as      |
|     |         |     |                       | and may be used or routinely          | described below under "Immune          |
|     |         |     |                       | modified to assess the ability of     | Activity", "Blood-Related              |
|     |         |     |                       | polypeptides of the invention         | Disorders", and/or "Cardiovascular     |
|     |         |     |                       | (including antibodies and agonists or | Disorders"). Preferred indications     |
|     |         |     |                       | antagonists of the invention) to      | include autoimmune diseases (e.g.,     |
|     |         |     |                       | regulate GATA3 transcription factors  | rheumatoid arthritis, systemic lupus   |
|     |         |     |                       | and modulate expression of mast cell  | erythematosis, multiple sclerosis      |
|     |         |     |                       | genes important for immune response   | and/or as described below) and         |
|     |         |     |                       | development. Exemplary assays for     | immunodeficiencies (e.g., as           |
|     |         |     |                       | transcription through the GATA3       | described below). Preferred            |
|     |         |     |                       | response element that may be used or  | indications include neoplastic         |
|     |         |     |                       | routinely modified to test GATA3-     | discases (e.g., leukemia, lymphoma,    |
|     |         |     |                       | response element activity of          | melanoma, prostate, breast, lung,      |
|     |         |     |                       | polypeptides of the invention         | colon, pancreatic, esophageal,         |
|     |         |     |                       | (including antibodies and agonists or | stomach, brain, liver, and urinary     |
|     |         |     |                       | antagonists of the invention) include | tract cancers and/or as described      |
|     |         |     |                       | assays disclosed in Berger et al.,    | below under "Hyperproliferative        |
|     |         |     |                       | Gene 66:1-10 (1998); Cullen and       | Disorders"). Other preferred           |
|     |         |     |                       | Malm, Methods in Enzymol              | indications include benign             |
|     |         |     |                       | 216:362-368 (1992); Henthorn et al.,  | dysproliferative disorders and pre-    |
|     |         |     |                       | Proc Natl Acad Sci USA 85:6342-       | neoplastic conditions, such as, for    |
|     |         |     |                       | 6346 (1988); Flavell et al., Cold     | example, hyperplasia, metaplasia,      |
|     |         |     |                       | Spring Harb Symp Quant Biol           | and/or dysplasia. Preferred            |
|     |         |     |                       | 64:563-571 (1999); Rodriguez-         | indications include anemia,            |
|     |         |     |                       | Palmero et al., Eur J Immunol         | pancytopenia, leukopenia,              |
|     |         |     |                       | 29(12):3914-3924 (1999); Zheng and    | thrombocytopenia, leukemias,           |
|     |         |     |                       | Flavell, Cell 89(4):587-596 (1997);   | Hodgkin's disease, acute               |

|     |         |     |                                                                       | response cheme activity of polypepids of the invention of polypepids of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:110 (1998); Cullen and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | melanoma, prostate, breast, lung, colon, pancratic, espolingal, storack, brain, liver, and urinary tract cancers and/or as described below under Hyperpolificative Disorders'). Other preferred indications include benign                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|---------|-----|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |         |     |                                                                       | 216:362-368 (1992). Heathom et al., 1990. Neal Acade (1988). Legal (1988). Legal (1988). Legal (1989). Legal (1989). Legal (1989). Acade (1989). Acade (1989). Acade (1989). Acade (1999). Acade (1999). Acade (1991). Acade (1991 | reaction that the condition of the condition of the condition, such as footbasic conditions, such as footbasic conditions, such as footbasic conditions, metaplasia, and/or dysplasia. Preferred and/or dysplasia. Preferred and/or dysplasia. Preferred punchiosytopenia, leukemias, puncytopenia, leukemias, leuke |
| 176 | HODDN92 | 580 | Activation of<br>Endothelial Cell p38 or<br>JNK Signaling<br>Pathway. | Kinasc assay. JNK and p38 kinasc assays for signal transkluction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | A highly preferred embodiment of<br>the invention includes a method for<br>stimulating endothelial cell growth.<br>An alternative highly preferred<br>embodiment of the invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| 4 19 4 1 2 2                                | 0.000                                   |
|---------------------------------------------|-----------------------------------------|
| modified to assess the ability of           | <b>a</b>                                |
| polypeptides of the invention               | endothelial cell growth. A highly       |
| (including antibodies and agonists or       | preferred embodiment of the             |
| antagonists of the invention) to            | invention includes a method for         |
| promote or inhibit cell proliferation,      | stimulating endothelial cell            |
| activation, and apoptosis. Exemplary        | proliferation. An alternative highly    |
| assays for JNK and p38 kinase               | preferred embodiment of the             |
| activity that may be used or routinely      | invention includes a method for         |
| modified to test JNK and p38 kinase-        | inhibiting endothelial cell             |
| induced activity of polypeptides of         | proliferation. A highly                 |
| the invention (including antibodies         | preferred embodiment of the             |
| and agonists or antagonists of the          | invention includes a method for         |
| invention) include the assays               | stimulating apoptosis of endothelial    |
| disclosed in Forrer et al., Biol Chem       | cells. An alternative highly preferred  |
| 379(8-9):1101-1110 (1998); Gupta et         | embodiment of the invention             |
| al., Exp Cell Res 247(2): 495-504           | includes a method for inhibiting (e.g., |
| (1999); Kyriakis JM, Biochem Soc            | decreasing) apoptosis of endothelial    |
| Symp 64:29-48 (1999); Chang and             | cells. A highly preferred               |
| Karin, Nature 410(6824):37-40               | embodiment of the invention             |
| (2001); and Cobb MH, Prog Biophys           | includes a method for stimulating       |
| Mol Biol 71(3-4):479-500 (1999);            | (e.g., increasing) endothelial cell     |
| the contents of each of which are           | activation. An alternative highly       |
| herein incorporated by reference in         | preferred embodiment of the             |
| its entirety. Endothelial cells that        | invention includes a method for         |
| may be used according to these              | inhibiting (e.g., decreasing) the       |
| assays are publicly available (e.g.,        | or ina                                  |
| through the ATCC <sup>TM</sup> ). Exemplary | endothelial cells. A highly             |
| endothelial cells that may be used          | preferred embodiment of the             |
| according to these assays include           | invention includes a method for         |
| human umbilical vein endothelial            | stimulating angiogenisis. An            |
| cells (HUVEC), which are                    | alternative highly preferred            |
| endothelial cells which line venous         | embodiment of the invention             |
| blood vessels, and are involved in          | includes a method for inhibiting        |
| functions that include, but are not         | angiogenesis. A highly preferred        |
| limited to, angiogenesis, vascular          | embodiment of the invention             |
| permeability, vascular tone, and            | includes a method for reducing          |
| immune cell extravasation.                  | cardiac hypertrophy. An alternative     |

| highly preferred embediment of the intensity of the area of the invention includes a method for indusing eardine hypertrophy.  Highly preferred indications include nopplastic diseases Eq. as described below under "Hyperproliferative Disorders"), and disorders of the | eardiovascular system (e.g., heart<br>disease, congestive heart failure,<br>hypertension, acuto stemosis,<br>eardiomyopalty, valvular<br>regungiation, left ventricular<br>dystimotion, atherosclerosis and<br>atherosclerotic vascular disease, | ularcuc, nephropany, intravaltuc<br>shart, actriac hypertrophy,<br>myo-actrial infarction, chronic<br>hemodynamic overloud, and or as<br>described below tunor as<br>described below tunor preferred infarctions. Ilighty<br>preferred infarctions include<br>cardiovascular ordeoletial and/or<br>angiogenic disorders (e.g., systemic<br>disorders that affect, vessels south as<br>disbarters that affect, vessels south as<br>disbarters that affect, vessels south as | utalector intelligists, with a sub-<br>ordine vessels themselves, such is of<br>the arterity, explinities, venus and or<br>lymphanics). Highly preferred are<br>infociations that stimulate<br>argiogenesis and/or<br>endiovascularization. Highly<br>preferred are indications that inhibit<br>argiogenesis and/or<br>endiovascularization. Highly<br>preferred indications include<br>artingagiogenic activity to treat solid<br>miningogenic activity to treat solid |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

|  | canonna and ratinal disordare          |
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|  | TI -11                                 |
|  | regalisms and amount methods           |
|  | Veneral and cancer, such as,           |
|  | Najvosi s saiconia, nemangionia        |
|  | (capillary and cavernous), glomus      |
|  | tumors, telangiectasia, bacillary      |
|  | angiomatosis,                          |
|  | hemangioendothelioma,                  |
|  | angiosarcoma,                          |
|  | haemangiopericytoma,                   |
|  | lymphangioma, lymphangiosarcoma,       |
|  | Highly preferred indications also      |
|  | include cancers such as, prostate,     |
|  | breast, lung, colon, pancreatic,       |
|  | esophageal, stomach, brain, liver,     |
|  | and urinary cancer. Preferred          |
|  | indications include benign             |
|  | dysproliferative disorders and pre-    |
|  | neoplastic conditions, such as, for    |
|  | example, hyperplasia, metaplasia,      |
|  | and/or dysplasia. Highly               |
|  | preferred indications also include     |
|  | arterial disease, such as,             |
|  | atherosclerosis, hypertension,         |
|  | coronary artery disease,               |
|  | inflammatory vasculitides,             |
|  | Reynaud"s disease and Reynaud"s        |
|  | phenomenom, aneurysms, restenosis;     |
|  | venous and lymphatic disorders such    |
|  | as thrombophlebitis, lymphangitis,     |
|  | and lymphedema; and other vascular     |
|  | disorders such as peripheral vascular  |
|  | disease, and cancer. Highly            |
|  | preferred indications also include     |
|  | trauma such as wounds, burns, and      |
|  | injured tissue (e.g., vascular injury  |
|  | such as, injury resulting from balloon |

| _ | angioplast                                   | angioplasty, and atheroschlerotic                                     |
|---|----------------------------------------------|-----------------------------------------------------------------------|
|   | kestons), ii                                 | lesions), implant fixation, scarring,<br>ischemia reperfusion iniury. |
|   | rhenmatoi                                    | rheumatoid arthritis, cerebrovascular                                 |
|   | disease, re                                  | disease, renal diseases such as acute                                 |
|   | renal failu                                  | renal failure, and osteoporosis.                                      |
|   | Additiona                                    | Additional highly preferred                                           |
|   | III/III/OII III/III/OII III/III/OII III/III/ | minications metude stroke, grant<br>rejection, diabetic or other      |
|   | retinopath                                   | retinopathies, thrombotic and                                         |
|   | coagulativ                                   | coagulative disorders, vascularitis,                                  |
|   | lymph ang                                    | lymph angiogenesis, sexual                                            |
|   | disorders,                                   | disorders, age-related macular                                        |
|   | degenerati                                   | degeneration, and treatment                                           |
|   | /preventio                                   | 'prevention of endometriosis and                                      |
|   | related co                                   | related conditions. Additional highly                                 |
|   | preferred                                    | preferred indications include                                         |
|   | fibromas,                                    | fibromas, heart disease, cardiac                                      |
|   | arrest, hea                                  | dis                                                                   |
|   | vascular disease.                            | disease. Preferred                                                    |
|   | indication                                   | indications include blood disorders                                   |
|   | (e.g., as de                                 | (e.g., as described below under                                       |
|   | "Immune                                      | "Immune Activity", "Blood-Related                                     |
|   | Disorders                                    | Disorders", and/or "Cardiovascular                                    |
|   | Disorders                                    | Disorders"). Preferred indications                                    |
|   | include au                                   | include autoimmune diseases (e.g.,                                    |
|   | rheumatoi                                    | rheumatoid arthritis, systemic lupus                                  |
|   | erythemat                                    | erythematosis, multiple sclerosis                                     |
|   | and/or as                                    | and/or as described below) and                                        |
|   | pounumi                                      | immunodeficiencies (e.g., as                                          |
|   | described                                    | described below). Additional                                          |
|   | preferred                                    | preferred indications include                                         |
|   | inflammat                                    | inflammation and inflammatory                                         |
|   | disorders                                    | disorders (such as acute and chronic                                  |
|   | inflammat                                    | inflammatory diseases, e.g.,                                          |
|   | inflammat                                    | inflammatory bowel disease and                                        |
|   | Crohn's d                                    | Crohn's disease), and pain                                            |

| management. | A highly preferred embodiment of<br>the invention includes a method for | increasing muscle cell survival An  | alternative highly preferred         | embodiment of the invention         | miscle cell survival A preferred                                 | 5                             | includes a method for stimulating     | muscle cell proliferation. In a  | specific embodiment, skeletal muscle | cell proliferation is stimulated. An | alternative highly preferred    | embodiment of the invention            | includes a method for inhibiting    | muscle cell proliferation. In a | specific embodiment, skeletal muscle | cell proliferation is inhibited. A | preferred embodiment of the            | invention includes a method for | stimulating muscle cell           | differentiation. In a specific      | embodiment, skeletal muscle cell | differentiation is stimulated. An    | alternative highly preferred | embodiment of the invention      | includes a method for inhibiting      | muscle cell differentiation. In a     | specific embodiment, skeletal muscle  | cell differentiation is inhibited.           | Highly preferred indications include | disorders of the musculoskeletal     | system. Preferred indications       | include neoplastic diseases (e.g., as | described below under            | "Hyperproliferative Disorders"),     |
|-------------|-------------------------------------------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------------------------------------------|-------------------------------|---------------------------------------|----------------------------------|--------------------------------------|--------------------------------------|---------------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------------|----------------------------------------|---------------------------------|-----------------------------------|-------------------------------------|----------------------------------|--------------------------------------|------------------------------|----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|----------------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------|--------------------------------------|
|             | Kinase assay. Kinase assays, for<br>example an GSK-3 kinase assay, for  | PI3 kinase signal transduction that | regulate glucose metabolism and cell | survivial are well-known in the art | and may be used or rounnely<br>modified to assess the ability of | polypeptides of the invention | (including antibodics and agonists or | antagonists of the invention) to | promote or inhibit glucose           | metabolism and cell survival.        | Exemplary assays for PI3 kinase | activity that may be used or routinely | modified to test PI3 kinase-induced | activity of polypeptides of the | invention (including antibodies and  | agonists or antagonists of the     | invention) include assays disclosed in | Forrer et al., Biol Chem 379(8- | 9):1101-1110 (1998); Nikoulina et | al., Diabetes 49(2):263-271 (2000); | and Schreyer et al., Diabetes    | 48(8):1662-1666 (1999), the contents | of each of which are herein  | incorporated by reference in its | entirety. Rat myoblast cells that may | be used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary rat myoblast | cells that may be used according to  | these assays include L6 cells. L6 is | an adherent rat myoblast cell line, | isolated from primary cultures of rat | thigh muscle, that fuses to form | multinucleated myotubes and striated |
|             | Activation of Skeletal<br>Mucle Cell P13 Kinase                         | Signalling Pathway                  |                                      |                                     |                                                                  |                               |                                       |                                  |                                      |                                      |                                 |                                        |                                     |                                 |                                      |                                    |                                        |                                 |                                   |                                     |                                  |                                      |                              |                                  |                                       |                                       |                                       |                                              |                                      |                                      |                                     |                                       |                                  |                                      |
|             | 581                                                                     |                                     |                                      |                                     |                                                                  |                               |                                       |                                  |                                      |                                      |                                 |                                        |                                     |                                 |                                      |                                    |                                        |                                 |                                   |                                     |                                  |                                      |                              |                                  |                                       |                                       |                                       |                                              |                                      |                                      |                                     |                                       |                                  |                                      |
|             | HODEJ32                                                                 |                                     |                                      |                                     |                                                                  |                               |                                       |                                  |                                      |                                      |                                 |                                        |                                     |                                 |                                      |                                    |                                        |                                 |                                   |                                     |                                  |                                      |                              |                                  |                                       |                                       |                                       |                                              |                                      |                                      |                                     |                                       |                                  |                                      |
|             | 177                                                                     |                                     |                                      |                                     |                                                                  |                               |                                       |                                  |                                      |                                      |                                 |                                        |                                     |                                 |                                      |                                    |                                        |                                 |                                   |                                     |                                  |                                      |                              |                                  |                                       |                                       |                                       |                                              |                                      |                                      |                                     |                                       |                                  |                                      |

| fibers after culture in differentiation | endocrine disorders (e g. as            |
|-----------------------------------------|-----------------------------------------|
| media.                                  | described below under "Endocrine        |
|                                         | Disorders"), neural disorders (e.g., as |
|                                         | described below under "Neural           |
|                                         | Activity and Neurological               |
|                                         | Diseases"), blood disorders (e.g., as   |
|                                         | described below under "Immune           |
|                                         | Activity", "Cardiovascular              |
|                                         | Disorders", and/or "Blood-Related       |
|                                         | Disorders"), immune disorders (e.g.,    |
|                                         | as described below under "Immune        |
|                                         | Activity"), and infection (e.g., as     |
|                                         | described below under "Infectious       |
|                                         | Disease"). A highly preferred           |
|                                         | indication is diabetes mellitus.        |
|                                         | An additional highly preferred          |
|                                         | indication is a complication            |
|                                         | associated with diabetes (e.g.,         |
|                                         | diabetic retinopathy, diabetic          |
|                                         | nephropathy, kidney disease (e.g.,      |
|                                         | renal failure, nephropathy and/or       |
|                                         | other diseases and disorders as         |
|                                         | described in the "Renal Disorders"      |
|                                         | section below), diabetic neuropathy,    |
|                                         | nerve disease and nerve damage (e.g,    |
|                                         | due to diabetic neuropathy), blood      |
|                                         | vessel blockage, heart disease,         |
|                                         | stroke, impotence (e.g., due to         |
|                                         | diabetic neuropathy or blood vessel     |
|                                         | blockage), seizures, mental             |
|                                         | confusion, drowsiness, nonketotic       |
|                                         | hyperglycemic-hyperosmolar coma,        |
|                                         | cardiovascular disease (e.g., heart     |
|                                         | disease, atherosclerosis,               |
|                                         | microvascular disease, hypertension,    |
|                                         | stroke, and other diseases and          |
|                                         | disorders as described in the           |

| _ | 2 3                                   | "Cardiovascular Disorders" section                                  |
|---|---------------------------------------|---------------------------------------------------------------------|
|   | 8 ·B                                  | disorders (as described in the                                      |
|   | F.                                    | "Endocrine Disorders" section                                       |
|   | 26.5                                  | below), neuropathy, vision<br>innairment (e g diabetic retinonathy  |
|   | an                                    | and blindness), ulcers and impaired                                 |
|   | W                                     | wound healing, infections (e.g.,                                    |
|   | ·ii -                                 | infectious diseases and disorders as                                |
|   | 9 0                                   | described in the "Infectious<br>Diseases," section below esnecially |
|   | 70                                    | of the urinary tract and skin), carpal                              |
|   | THE PERSON NAMED IN                   | tunnel syndrome and Dupuytren's                                     |
|   | 3                                     | contracture). An additional                                         |
|   | <u>H</u>                              | highly preferred indication is obesity                              |
|   | an                                    | and/or complications associated with                                |
|   | qo                                    | obesity. Additional highly preferred                                |
|   | -ü-                                   | indications include weight loss or                                  |
|   | all                                   | alternatively, weight gain.                                         |
|   | W.                                    | Additional highly preferred                                         |
|   | · · · · · · · · · · · · · · · · · · · | indications are complications                                       |
|   | as                                    | associated with insulin resistance.                                 |
|   | <u> </u>                              | Additonal highly preferred                                          |
|   | .a                                    | indications are disorders of the                                    |
|   | m m                                   | musculoskeletal system including                                    |
|   | <u>a</u>                              | myopathies, muscular dystrophy,                                     |
|   | an                                    | and/or as described herein.                                         |
|   | AC.                                   | Additional highly preferred                                         |
|   | <u>.a.</u>                            | indications include: myopathy,                                      |
|   | ati                                   | atrophy, congestive heart failure,                                  |
|   | ca                                    | cachexia, myxomas, fibromas,                                        |
|   | 3                                     | congenital cardiovascular                                           |
|   | ap                                    | abnormalities, heart disease, cardiac                               |
|   | an                                    | arrest, heart valve disease, and                                    |
|   | Na Na                                 | vascular disease. Highly                                            |
|   | pr                                    | preferred indications include                                       |
|   | 90                                    | peoplasms and cancer such as                                        |

| _           |                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | urinary cancer. Preferred indications also include breast, Imag, colon, panceatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-nooplastic conditions, such as, hyperplastia, metaplastia, andor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HOPMQ33 582 | Regulation of viability and positional of paracratic beta cells, paracratic beta cells, | and provident to the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the country of the | the high proferred indication is dishers a relational and proferred indication is an inglety preferred indication is an inglety preferred indication is an inglety preferred indication is an opposition and include the proferred indication in the dishers to exposition of the season and societies with the dishers to exposition of the season and described in the 'Reall Disouthers' and and or other diseases and discrete as described in the 'Reall Disouthers' merve disease and nerve damage (e.g., the to disherio encopathy, heavy disease and nerve damage of exact inspense, e.g., the total district encopathy or blood vessel blockage, hearted insease, imperations on the season of the provision, thousains of the provision of the season, hypercastion curdownscular disease, hypercastion, stroke, and other diseases and references in the curdownscular Disouther's section disorders is described in the 'Cardiownscular Disouther's section disorders (see cheering disorders) section disorders (see discribed in the disorders). |

| n d                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | d .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| impainment (e.g., diabetic retinopality vision impainment (e.g., diabetic retinopality and hindress) ulcers and impaind wound healing, and infection (e.g., infections decones and disorders as infections decones and desorders and behavioral Diseases' section below, especially untuel syndrome and Dispuyers is contented by Androme and Dispuyers is productived in dictation is obesity and/or obesity. Additional highly preferred indications include weight loss or alternatively, weight deep weight loss or alternatively, weight weight loss or alternatively, weight weight loss or alternatively, weight weight loss or complications associated with insulin resistance.                                                                                                                                                                                                                            | A highly perferred embediment of the invention includes a method for a similaring adiptycyte professor and adiptycyte professor and include professor and include in invention includes a method for inthining adiptycyte for and includes a method for inthining adiptycyte for the invention includes a method for inthining adiptycyte of the invention includes a method of the invention includes a method for inhibiting adiptycyte of the invention includes a method for inhibiting adiptycyte of the invention includes a method for inhibiting adiptycyte of the invention includes a method for inhibiting preferred embodiment of the invention preferred embodiment of the inhibiting preferred embodiment of the inhibiting and preferred embodiment of the inhibiting and includes a method for inhibiting and preferred embodiment of the inhibiting and includes a method for inhibiting and preferred embodiment of the inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and includes a method for inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and inhibiting and i |
| is entirety. Pancreaic cells that me the extense in its entirety. Pancreaic cells that me to used according to these assays are publicly evanible (e.g., through the ATCC**) and four may be used according to these assays included personal Examplary pancreaide cells that may be used according to these assays include HIITTI S Cells. HIITTI is are an established from Syrian humster islet cashibished from Syrian humster is cells express glacagon, somanostanin or edit socrete insulin, which is stimulated by glucose and glucose and glucose and glucose insulin, which is stimulated by glucose and glucose insulin. 1. 219: 547-551; Santerre et al. Proc. 1. 219: 547-551; Santerre et al. Proc. 1. 218. All Acad. Sci. USA 78: 4339-4343. | the counties easy, for the counties easy, for the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of the counties of  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Adrigues of Adrigues of Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 583                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HOHBY44                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 6/1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| _ |  | (e.g., renal failure, nephropathy      |
|---|--|----------------------------------------|
|   |  | and/or other diseases and disorders as |
|   |  | described in the "Renal Disorders"     |
|   |  | section below), diabetic neuropathy,   |
|   |  | nerve disease and nerve damage         |
|   |  | (e.g., due to diabetic neuropathy),    |
|   |  | blood vessel blockage, heart disease,  |
|   |  | stroke, impotence (e.g., due to        |
|   |  | diabetic neuropathy or blood vessel    |
|   |  | blockage), seizures, mental            |
|   |  | confusion, drowsiness, nonketotic      |
|   |  | hyperglycemic-hyperosmolar coma,       |
|   |  | cardiovascular disease (e.g., heart    |
|   |  | disease, atherosclerosis,              |
|   |  | microvascular disease, hypertension,   |
|   |  | stroke, and other diseases and         |
|   |  | disorders as described in the          |
|   |  | "Cardiovascular Disorders" section     |
|   |  | below), dyslipidemia, endocrine        |
|   |  | disorders (as described in the         |
|   |  | "Endocrine Disorders" section          |
|   |  | below), neuropathy, vision             |
|   |  | impairment (e.g., diabetic retinopathy |
|   |  | and blindness), ulcers and impaired    |
|   |  | wound healing, infection (e.g.,        |
|   |  | infectious diseases and disorders as   |
|   |  | described in the "Infectious           |
|   |  | Diseases" section below (particularly  |
|   |  | of the urinary tract and skin). An     |
|   |  | additional highly preferred indication |
|   |  | is obesity and/or complications        |
|   |  | associated with obesity. Additional    |
|   |  | highly preferred indications include   |
|   |  | weight loss or alternatively, weight   |
|   |  | gain. Additional highly                |
|   |  | preferred indications are              |
|   |  | commitment accordated with inculin     |

| preferred indications are desirance, resistance, resistance, resistance, in musualistical systems including amyopathies, musualit desirational representation of the properties including myopathies, musualit desiration and preferred indicational inglidy preferred indicational inglidy, hypertension, coronary article, hypertension, coronary article, hypertension, coronary article, hypertension, coronary and letancy disease, obsilionaring, allismoss, ossionaring, and letancy diseases or disorders. Preferred indications include mobilisms and cuerc, such as your proplement, endered; and head of the proplement of the proposition of the proplement of the proposition of the proposition of the proposition of the proposition of the proposition include benging dystolificative desirades and propositions; include bengin and locations; include bengin dystolificative desirades and proposition conditions, and his for example, hyperplissis, metaplissis, and applied to the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition o | orontains<br>ence of<br>st specific<br>in specific<br>of which<br>of which                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Reporter Assay construct contains regulatory and coding sequence of exputers synthesize, the first specific entryme in the cholestron his synthesic pathway. See Jiang, et al., T Hoof Green 2 68:1288; 17824 (1993), the contents of which are therein morphorated by reference in its entirety. Cells were treated in its entirety. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Inhibition of squalene synthetase gene transcription.                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 584                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HOQBI82                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 180                                                                                                                                                                                                                                                                                                                                   |

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|     |         |     |                        | 4:193-204 (1999), the contents of      | wound healing, and infection (e.g.,    |
|-----|---------|-----|------------------------|----------------------------------------|----------------------------------------|
|     |         |     |                        | each of which is herein incorporated   | infectious diseases and disorders as   |
|     |         |     |                        | by reference in its entirety.          | described in the "Infectious           |
|     |         |     |                        | Pancreatic cells that may be used      | Diseases" section below, especially    |
|     |         |     |                        | according to these assays are publicly | of the urinary tract and skin), carpal |
|     |         |     |                        | available (e.g., through the ATCCTM)   | 9                                      |
|     |         |     |                        | and/or may be routinely generated.     | contracture). An additional            |
|     |         |     |                        | Exemplary pancreatic cells that may    | highly preferred indication is obesity |
|     |         |     |                        | be used according to these assays      | and/or complications associated with   |
|     |         |     |                        | include HITT15 Cells. HITT15 are       | obesity. Additional highly preferred   |
|     |         |     |                        | an adherent epithelial cell line       | indications include weight loss or     |
|     |         |     |                        | established from Syrian hamster islet  | alternatively, weight gain. Additional |
|     |         |     |                        | cells transformed with SV40. These     | highly preferred indications are       |
|     |         |     |                        | cells express glucagon, somatostatin,  | complications associated with insulin  |
|     |         |     |                        | and glucocorticoid receptors. The      | resistance.                            |
|     |         |     |                        | cells secrete insulin, which is        |                                        |
|     |         |     |                        | stimulated by glucose and glucagon     |                                        |
|     |         |     |                        | and suppressed by somatostatin or      |                                        |
|     |         |     |                        | glucocorticoids. ATTC# CRL-1777        |                                        |
|     |         |     |                        | Refs: Lord and Ashcroft. Biochem.      |                                        |
|     |         |     |                        | J. 219: 547-551; Santerre et al. Proc. |                                        |
|     |         |     |                        | Natl. Acad. Sci. USA 78: 4339-4343,    |                                        |
|     |         |     |                        | 1981.                                  |                                        |
|     | HOSBY40 | 585 | Regulation of          | Assays for the regulation of           | A highly preferred indication is       |
| 181 |         |     | transcription through  | transcription through the FAS          | diabetes mellitus. An                  |
|     |         |     | the FAS promoter       | promoter element are well-known in     | additional highly preferred indication |
|     |         |     | element in hepatocytes | the art and may be used or routinely   | is a complication associated with      |
|     |         |     |                        | modified to assess the ability of      | diabetes (e.g., diabetic retinopathy,  |
|     |         |     |                        | polypeptides of the invention          | diabetic nephropathy, kidney disease   |
|     |         |     |                        | (including antibodies and agonists or  | (e.g., renal failure, nephropathy      |
|     |         |     |                        | antagonists of the invention) to       | and/or other diseases and disorders as |
|     |         |     |                        | activate the FAS promoter element in   | described in the "Renal Disorders"     |
|     |         |     |                        | a reporter construct and to regulate   | section below), diabetic neuropathy,   |
|     |         |     |                        | transcription of FAS, a key enzyme     | nerve disease and nerve damage         |
|     |         |     |                        | for lipogenesis. FAS promoter is       | (e.g., due to diabetic neuropathy),    |
|     |         |     |                        | regulated by many transcription        | blood vessel blockage, heart disease,  |
|     |         |     |                        | factors including SREBP. Insulin       | stroke, impotence (e.g., due to        |

|    |     |                      | increases FAS gene transcription in     | diabetic neuropathy or blood vessel    |
|----|-----|----------------------|-----------------------------------------|----------------------------------------|
|    |     |                      | livers of diabetic mice. This           | blockage), seizures, mental            |
|    |     |                      | stimulation of transcription is also    | confusion, drowsiness, nonketotic      |
|    |     |                      | somewhat glucose dependent.             | hyperglycemic-hyperosmolar coma,       |
|    |     |                      | Exemplary assays that may be used       | cardiovascular disease (e.g., heart    |
|    |     |                      | or routinely modified to test for FAS   | disease, atherosclerosis,              |
|    |     |                      | promoter element activity (in           | microvascular disease, hypertension,   |
|    |     |                      | hepatocytes) by polypeptides of the     | stroke, and other diseases and         |
|    |     |                      | invention (including antibodies and     | disorders as described in the          |
|    |     |                      | agonists or antagonists of the          | "Cardiovascular Disorders" section     |
|    |     |                      | invention) include assays disclosed in  | below), dyslipidemia, endocrine        |
|    |     |                      | Xiong, S., et al., Proc Natl Acad Sci   | disorders (as described in the         |
|    |     |                      | U.S.A., 97(8):3948-53 (2000);           | "Endocrine Disorders" section          |
|    |     |                      | Roder, K., et al., Eur J Biochem,       | below), neuropathy, vision             |
|    |     |                      | 260(3):743-51 (1999); Oskouian B,       | impairment (e.g., diabetic retinopathy |
|    |     |                      | et al., Biochem J, 317 (Pt 1):257-65    | and blindness), ulcers and impaired    |
|    |     |                      | (1996); Berger, et al., Gene 66:1-10    | wound healing, and infection (e.g.,    |
|    |     |                      | (1988); and, Cullen, B., et al.,        | infectious diseases and disorders as   |
|    |     |                      | Methods in Enzymol. 216:362-368         | described in the "Infectious           |
|    |     |                      | (1992), the contents of each of which   | Diseases" section below, especially    |
|    |     |                      | is herein incorporated by reference in  | of the urinary tract and skin), carpal |
|    |     |                      | its entirety. Hepatocytes that may be   | tunnel syndrome and Dupuytren's        |
|    |     |                      | used according to these assays, such    | contracture). An additional            |
|    |     |                      | as H4IIE cells, are publicly available  | highly preferred indication is obesity |
|    |     |                      | (e.g., through the ATCCTM) and/or       | and/or complications associated with   |
|    |     |                      | may be routinely generated.             | obesity. Additional highly preferred   |
|    |     |                      | Exemplary hepatocytes that may be       | indications include weight loss or     |
|    |     |                      | used according to these assays          | alternatively, weight gain.            |
|    |     |                      | include rat liver hepatoma cell line(s) | Aditional highly preferred             |
|    |     |                      | inducible with glucocorticoids,         | indications are complications          |
|    |     |                      | insulin, or cAMP derivatives.           | associated with insulin resistance.    |
| 88 | 989 | Production of ICAM-1 | Assays for measuring expression of      | Preferred embodiments of the           |
|    |     |                      | ICAM-1 are well-known in the art        | invention include using polypeptides   |
|    |     |                      | and may be used or routinely            | of the invention (or antibodies,       |
|    |     |                      | modified to assess the ability of       | agonists, or antagonists thereof) in   |
|    |     |                      | polypeptides of the invention           | detection, diagnosis, prevention,      |
|    |     |                      | (including antibodies and agonists or   | and/or treatment of Vascular Disease,  |

| Atherocalerosis, Resternosis, Stroke, and Ashtma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | include blood disorders (e.g., as excepted by the disorders) (e.g., as excepted below under "fumme Activity", "Blood-kelased blood-to-funderse," and softwards, and softwards include autoimmune indications include autoimmune indications include autoimmune indications include autoimmune systemic lupus crytheninosis, systemic lupus crytheninosis, systemic lupus crytheninosis, systemic lupus crytheninosis, and multiple schenics (e.g., as accepted below), immune response, and mediated immune response, and elleriaediated immune response, and immune response and immune response.                                                                                                                                                                       |
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| amtagonists of the invention) to Exemplary assays that may be used required (TAM-1 expression Further and the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management of the management | treassary for the extraction of reassary for the extraction of a contract of cold (VEAT) response element are well-known in response element are well-known in modified to suesses the ability of polypeptides of the invention of polypeptides and agonists or the invention) to an analysis of the invention) to an analysis of the invention) to an analysis of the invention) to an analysis of the invention) to an analysis of the invention) to a magnonists of the invention) to a magnonist of the invention) to accompanie only a formation of genes and modifiate expression of genes and modifiate expression of genes and modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the modifiate expression of genes in the genera |
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| A highly preferred indication is                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | is Caspase Apoptosis. Assays for       | Regulation of apoptosis | 989 | HOSD125 |  |
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| Disease asthma and alleroy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |                         |     |         |  |
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| organis and ussues, nemopunia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                        |                         |     |         |  |
| of immune reactions to transplanted                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                        |                         |     |         |  |
| neutrophilia, psoriasis, suppression                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | _                                      |                         |     | _       |  |
| bowel disease, sepsis, neutropenia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                        |                         |     |         |  |
| granulomatous disease, inflammatory                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                        |                         |     |         |  |
| Burkitt's lymphoma, arthritis, AIDS,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | activity.                              |                         |     |         |  |
| plasmacytomas, multiple myeloma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | cell line with cytolytic and cytotoxic |                         |     |         |  |
| lymphocytic anemia (ALL),                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | line, which is a human natural killer  |                         |     |         |  |
| Hodgkin's disease, acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | these assays include the NK-YT cell    |                         |     |         |  |
| leukopenia, thrombocytopenia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | cells that may be used according to    |                         |     |         |  |
| dyspiasia, rreterred indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | ATCTM Evamples; himong inc             |                         |     |         |  |
| hyperplasia, metaplasia, and/or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | used according to these assays are     |                         |     |         |  |
| conditions, such as, for example,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | its entirety. NK cells that may be     |                         |     |         |  |
| disorders and pre-neoplastic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | herein incorporated by reference in    |                         |     |         |  |
| include benign dysproliferative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | the contents of each of which are      |                         |     |         |  |
| cancer. Other preferred indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Chem 268(19):14285-14293 (1993),       |                         |     |         |  |
| stomach, brain, liver and urinary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | (1999); and Yeseen et al., J Biol      |                         |     |         |  |
| colon, pancreatic, esophageal,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | al., Eur J Immunol 29(3):838-844       |                         |     |         |  |
| lymphoma, and prostate, breast, lung,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 31(10):1221-1236 (1999); Fraser et     |                         |     |         |  |
| as, for example, leukemia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Boer et al., Int J Biochem Cell Biol   |                         |     |         |  |
| include neoplasms and cancers, such                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Med 182(3):801-810 (1995); De          |                         |     |         |  |
| Disorders"). Preferred indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 6346 (1988); Aramburu et al., J Exp    |                         |     |         |  |
| below under "Hyperproliferative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Proc Natl Acad Sci USA 85:6342-        |                         |     |         |  |
| lymphoma, and/or as described                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 216:362-368 (1992); Henthorn et al.,   |                         |     |         |  |
| neoplastic diseases (e.g., leukemia,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Malm, Methods in Enzymol               |                         |     |         |  |
| Preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Gene 66:1-10 (1998); Cullen and        |                         |     |         |  |
| below under "Infectious Disease").                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | assays disclosed in Berger et al       |                         |     |         |  |
| an infectious disease as described                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | antagonists of the invention) include  |                         |     |         |  |
| preferred indication is infection (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | (including antibodies and agonists or  |                         |     |         |  |
| disorders. An additional highly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | polypeptides of the invention          |                         |     |         |  |
| inflammation and inflammatory                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | response element activity of           |                         |     |         |  |
| preferred indications include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | routinely modified to test NFAT-       |                         |     |         |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                        |                         |     |         |  |

| diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetto retinopathy, diabetes (e.g., diabetto retinopathy, diabetic a feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet of the feet | e.g. rent anturb. reptropound and or checkers as section below), diabetic neuropathy, are viewed and reve disease and turve disease and arre disease and arre disease and arre disease and arre disease. The blood vessel blocking, heart disease, the whole of the property of the checkers are the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of 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| caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or the case of the control of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case of the case | antagonais on the Urezinon) to a<br>promote caspase protease-mediated apoptosis. 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(1997), Zimeg, 2. et al., FEBS Lett, 455(2);315-30 (1999); Lee et al., 455(3);315-30 (1999); Lee et al |
| in pancreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| obesity. Additional highly preferred indications associated with obesity. Additional highly preferred indications metude weight gain. Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                          | A highly preferred embeliment of the invention includes a method for strainhaing aginocyce professional and a farmative highly preferred embediment of the invention includes a method for inhibiting adipocyc profileration. An alternative profileration when the profession includes a method for inhibiting adipocyc profileration of the invention includes a method for inhibiting adipocyc differentiation. An alternative highly preferred embediment of the invention includes a method for inhibiting and proper differentiation. An alternative highly preferred embediment of the invention includes a method for inhibiting and invention includes a method for a simulating (e.g. increasing) and for includes a method for inhibiting the activation. An alternative includes a method for invention includes a method for invention includes a method for invention includes a method for invention includes a method for invention includes a method for invention includes a method for invention includes includes includes and includes includes and includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes includes inclu |
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| rough the ATCV'en and/or may be nourisely generated. Exemplary paracreatic cells that may be used to according to these seasys include RNA-m. RNA-m is a real additionancell line derived from a radiation induced line derived from a radiation induced line derived from a radiation induced line derived from a radiation induced line clerived from a radiation induced line clerived from a radiation induced line clerived from a radiation induced insulin, sommostanti, and possibly deapends. The cells proude et al. Proc. Natl. Acad. Sci. 1977 14-628, A feet al. Proc. Natl. Acad. Sci. Acad. Sci. 1980 773519. | coumple an Ille! Itimes assay, for example an Ille! Itimes assay, for a file of the second of the second of the second of the second of the second of the second of the second of the second or outlied you defined an assay the ability of polypeptides of the intervient of the delinging anthodics and agonisis or anagonisis of the the second of the second of the second of the second or the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Addravien of Addravien of Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| t, adipocytes. Highly preferred ); indications include endocrine disorders (e.g., as described below under "findocrine Disorders").      | Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as |                                                                                                      | disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, immortance and/or as discerbed halow |                                                                                                            | disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g. as described below   |                                                                     | desc<br>Dise | diabetes melitus. An additional highly preferred indication is a complication associated with | diabetes (e.g., diabetic retinopathy,<br>diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy<br>and/or other diseases and disorders as | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropatity),<br>blood vessel blockage heart disease |
|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------|--------------------------------|-----------------------------------------------------------------------------|
| 107(2):126-132 (1999), Kyriakis JM,<br>Biochem Soc Symp 64:29-48 (1999);<br>Chang and Karin, Nature<br>410(68/24):37-40 (2001); and Cohb | MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein            | incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these | assays are publicly available (e.g., through the ATCCTA). Exemplary mouse adjoocyte cells that may be used accounting to those assays.      | include 373-L1 cells. 373-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of | 3T3 fibroblast cells developed<br>through clonal isolation and undergo<br>a pre-adimocyte to adimose-like | conversion under appropriate<br>differentiation conditions known in | the art.     |                                                                                               |                                                                               |                                                                             |                                      |                                |                                                                             |
|                                                                                                                                          |                                                                                                       |                                                                                                      |                                                                                                                                             |                                                                                                            |                                                                                                           |                                                                     |              |                                                                                               |                                                                               |                                                                             |                                      |                                |                                                                             |
|                                                                                                                                          |                                                                                                       |                                                                                                      |                                                                                                                                             |                                                                                                            |                                                                                                           |                                                                     |              |                                                                                               |                                                                               |                                                                             |                                      |                                | _                                                                           |

|  |  | stroke, innotence (e.g., due to        |
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|  |  | dishetic neuronathy or blood vessel    |
|  |  | blockage) saigness mental              |
|  |  | confusion decursings nonfatotic        |
|  |  | contusion, arowaniess, nonvecoure      |
|  |  | hyperglycemic-hyperosmolar coma,       |
|  |  | cardiovascular disease (e.g., heart    |
|  |  | disease, atherosclerosis,              |
|  |  | microvascular disease, hypertension,   |
|  |  | stroke, and other diseases and         |
|  |  | disorders as described in the          |
|  |  | "Cardiovascular Disorders" section     |
|  |  | below), dyslipidemia, endocrine        |
|  |  | disorders (as described in the         |
|  |  | "Endocrine Disorders" section          |
|  |  | below), neuropathy, vision             |
|  |  | impairment (e.g., diabetic retinopathy |
|  |  | and blindness), ulcers and impaired    |
|  |  | wound healing, infection (e.g.,        |
|  |  | infectious diseases and disorders as   |
|  |  | described in the "Infectious           |
|  |  | Diseases" section below (particularly  |
|  |  | of the urinary tract and skin). An     |
|  |  | additional highly preferred indication |
|  |  | is obesity and/or complications        |
|  |  | associated with obesity. Additional    |
|  |  | highly preferred indications include   |
|  |  | los                                    |
|  |  | gain. Additional highly                |
|  |  | preferred indications are              |
|  |  | complications associated with insulin  |
|  |  | resistance. Additional highly          |
|  |  | preferred indications are disorders of |
|  |  | the musculoskeletal systems            |
|  |  | including myopathies, muscular         |
|  |  | dystrophy, and/or as described         |
|  |  | herein. Additional highly              |
|  |  | preferred indications include,         |

| disperses on coronary streyy disperses, dospindennia, galisones, ostooarthiis, degenerative arthritis, and gloodes, fibrosis, eachexia, and klainey diseases or disooders. Through an and carbor, south as, prophisms and earbor, soith as, prophisms and earbor, south as, thorpional, lederaged, alsomed, melanomia, prostate, lung, melanomia, prostate, lung, melanomia, prostate, lung, melanomia, prostate, lung, melanomia, prostate, and unimary cancer. Highly preferred indications include bring preferred indications include bring preferred indications include bring preferred indications include bring preferred indications, said as, for morphistic conditions, said as, for morphistic conditions, said as, for and/or dysplasia, metaplasia, | referred embodiments of the invention include using polyperides of the invention (or antibodies, or antipolis as agonists, or antagonists the article of detection, diagnosis, prevention, and/or treatment of asthma, allergy, hypersensitivity and inflammation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | proliferation of proliferation and/or for the control of the control or intransic cells (such as mast cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 587                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | H0UCQ17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 183                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | allegy, sestion diductations include allegy, sestion, and other diductions and additional preferred indications. Additional preferred indications included incitors (e.g., an intection disease is described below under inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammati |
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| angendused to the invention) included the masspot sideshood in: All 11, ct al. [1, ct al. 2000); Tammod, 16(21)/22(5-22) and 19(20); Tammod, 16(21)/22(5-22) and 19(20); Bayl, Lagor et al. Biod. Come 139(8-9); 110-1110 (1998); Deme et al. Biochem 139(8-9); 110-1110 (1998); Deme et al. Biochem 139(8-9); 110-1110 (1998); Deme et al. Biochem 13, Tayl 2000; 110-112 (2000); Tammod 16(9); 110-112 (2000); Tammod 16(9); Tayl 2000; Paul Code MHI, Prog Biophys Mol Biod 71(2-4)-29-500 (1999); Mol Biod 71(2-4)-29-500 (1999); Tammod Paul Paul Paul Paul Paul Paul Paul Paul | activation of the GATA-3 signaling pathway in HMC-1 human mast cell in Activation of GATA-3 in mast cells has been linked to cytokine and cells has been linked to cytokine and cells has been linked to cytokine and the control of the mascription of transcription and may be used or routinely modified to assess the ability of polypeptides of the invention of polypeptides of the invention in continuing amplicates and the invention in the analysis of the invention in the continuing amplieds and agonts or autagonists of the invention) to graphing CATA-3 in the invention of mast cell and confined expression of mast cell and collaborate and continued to the continued of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration of the collaboration |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Activation of Activation of Iranscription through (GATA-3) regionse clement in immune cells (such as mast cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2887                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HOUCQ17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 183                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                       | transcription through the GATA3            | described helow) Preferred           |
|-----|---------|-----|-----------------------|--------------------------------------------|--------------------------------------|
|     |         |     |                       | response element that may be used or       | indications include neoplastic       |
|     |         |     |                       | routinely modified to test GATA3-          | discases (e.g., leukemia, lymphoma,  |
|     |         |     |                       | response element activity of               | melanoma, prostate, breast, lung,    |
|     |         |     |                       | polypeptides of the invention              | colon, pancreatic, esophageal,       |
|     |         |     |                       | (including antibodies and agonists or      | stomach, brain, liver, and urinary   |
|     |         |     |                       | antagonists of the invention) include      | tract cancers and/or as described    |
|     |         |     |                       | assays disclosed in Berger et al.,         | below under "Hyperproliferative      |
|     |         |     |                       | Gene 66:1-10 (1998); Cullen and            | Disorders"). Other preferred         |
|     |         |     |                       | Malm, Methods in Enzymol                   | indications include benign           |
|     |         |     |                       | 216:362-368 (1992); Henthorn et al.,       | dysproliferative disorders and pre-  |
|     |         |     |                       | Proc Natl Acad Sci USA 85:6342-            | neoplastic conditions, such as, for  |
|     |         |     |                       | 6346 (1988); Flavell et al., Cold          | example, hyperplasia, metaplasia,    |
|     |         |     |                       | Spring Harb Symp Quant Biol                | and/or dysplasia. Preferred          |
|     |         |     |                       | 64:563-571 (1999); Rodriguez-              | indications include anemia,          |
|     |         |     |                       | Palmero et al., Eur J Immunol              | pancytopenia, leukopenia,            |
|     |         |     |                       | 29(12):3914-3924 (1999); Zheng and         | thrombocytopenia, leukemias,         |
|     |         |     |                       | Flavell, Cell 89(4):587-596 (1997);        | Hodgkin's disease, acute             |
|     |         |     |                       | and Henderson et al., Mol Cell Biol        | lymphocytic anemia (ALL),            |
|     |         |     |                       | 14(6):4286-4294 (1994), the contents       | plasmacytomas, multiple myeloma,     |
|     |         |     |                       | of each of which are herein                | Burkitt's lymphoma, arthritis, AIDS, |
|     |         |     |                       | incorporated by reference in its           | granulomatous disease, inflammatory  |
|     |         |     |                       | entirety. Mast cells that may be used      | bowel disease, sepsis, neutropenia,  |
|     |         |     |                       | according to these assays are publicly     | neutrophilia, psoriasis, suppression |
|     |         |     |                       | available (e.g., through the               | of immune reactions to transplanted  |
|     |         |     |                       | ATCC <sup>TM</sup> ). Exemplary human mast | organs and tissues, hemophilia,      |
|     |         |     |                       | cells that may be used according to        | hypercoagulation, diabetes mellitus, |
|     |         |     |                       | these assays include the HMC-1 cell        | endocarditis, meningitis, and Lyme   |
|     |         |     |                       | line, which is an immature human           | Disease.                             |
|     |         |     |                       | mast cell line established from the        |                                      |
|     |         |     |                       | peripheral blood of a patient with         |                                      |
|     |         |     |                       | mast cell leukemia, and exhibits           |                                      |
|     |         |     |                       | many characteristics of immature           |                                      |
|     |         |     |                       | mast cells.                                |                                      |
|     | HOUCQ17 | 587 | Activation of         | This reporter assay measures               | Highly preferred indications include |
| 183 |         |     | transcription through | activation of the NFAT signaling           | allergy, asthma, and rhinitis.       |
|     |         |     | NFAT response         | pathway in HMC-1 human mast cell           | Additional preferred indications     |
|     |         |     |                       |                                            |                                      |

| include infection (e.g., an infectious<br>disease as described below under | "Infectious Disease"), and<br>inflammation and inflammatory         | disorders. Preferred indications also | include blood disorders (e.g., as | described below under immune<br>Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications | include autoimmune diseases (e.g.,    | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis   | and/or as described below) and   | immunodeficiencies (e.g., as | described below). Preferred     | indications include neoplastic | diseases (e.g., leukemia, lymphoma,  | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary | tract cancers and/or as described     | below under "Hyperproliferative       | Disorders"). Other preferred       | indications include benign      | dysproliferative disorders and pre- | neoplastic conditions, such as, for  | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred        | indications include anemia,        | pancytopenia, leukopenia,     | thrombocytopenia, leukemias, | Hodgkin's disease, acute         | lymphocytic anemia (ALL),        | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory |
|----------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------|-----------------------------------|-----------------------------------------------------------|------------------------------------|------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|----------------------------------|------------------------------|---------------------------------|--------------------------------|--------------------------------------|-----------------------------------|--------------------------------|------------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|------------------------------------|-------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|
| line. Activation of NFAT in mast<br>cells has been linked to cytokine and  | chemokine production. Assays for<br>the activation of transcription | through the Nuclear Factor of         | Activated T cells (NFAT) response | and may be used or routinely                              | modified to assess the ability of  | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to     | regulate NFAT transcription factors | and modulate expression of genes | involved in immunomodulatory | functions. Exemplary assays for | transcription through the NFAT | response element that may be used or | routinely modified to test NFAT-  | response element activity of   | polypeptides of the invention      | (including antibodics and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol            | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-   | 6346 (1988); De Boer et al., Int J | Biochem Cell Biol 31(10):1221-1236 | (1999); Ali et al., J Immunol | 165(12):7215-7223 (2000);    | Hutchinson and McCloskey, J Biol | Chem 270(27):16333-16338 (1995), | and Turner et al., J Exp Med     | 188:527-537 (1998), the contents of  | each of which are herein            |
| cells (such as mast                                                        | cells).                                                             |                                       |                                   |                                                           |                                    |                                    |                                       |                                      |                                     |                                  |                              |                                 |                                |                                      |                                   |                                |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |                                  |                                      |                                     |
|                                                                            |                                                                     |                                       |                                   |                                                           |                                    |                                    |                                       |                                      |                                     |                                  |                              |                                 |                                |                                      |                                   |                                |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |                                  |                                      |                                     |

| developeration of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the | o a II per ui .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| emorporated by reference in the emorporated by reference in the emorphism of a school of the form of the ATC'N'. Exemplary human mast cold in the map we losed soon of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of a patient human mast cell the school of a patient with must cell teakernit, and exhibits must chance the school of a patient with must cell teakernit, and exhibits must chance the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the school of the schoo | sayes for the gentlation (i.e., increases) or decreases) of viability and proliferation or cleals in vitum are well-known in the art and may be used or routinely modified to assess the ability of polyperdides of the mention (including antibodes and mention) to regulate whellity and organise or anapolication of pre-adionse cells and ell lines. For example, the cell function of the mention of the medical polyperdides of the invention) to regulate whellity and cell lines. For example, the cell function of the medical polyperdides of the medical polyperdides of the medical polyperdides of the medical polyperdides of the medical polyperdides of the medical polyperdides of the medical polyperdides of mentionically active collure based on quantitation of the presence of mentionically active continuous sharing of \$173\$ flipols active continuous sharing of \$173\$ flipols active cells developed through cells and adpose cells asteried to an adpose lets asteried to an adpose like state. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adipose cells (such as 3T3-L1 cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 287                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HOUCQ17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 183                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is breein incorporated by reference in its entirety. | immunomodulatory proteins that inturbuse derivatives that inturbuse derivatives of T cells, monocycs, and consophilis are well monocycs, and consophilis are well monocycs, and consophilis are well monocycs, and composible to use asset the ability of polyspeddes of the ability of polyspeddes of the ability of polyspeddes of the immunomodulation, induce immunomodulation, induce immunomodulation, induce of cell-incidiated immunity, and the state of the immunomodulation of cell-incidiated immunity of cell-incidiated immunity and the state of the immunomodulatory proteins evaluate immunomodulatory proteins evaluate immunomodulatory proteins evaluate immunomodulatory proteins evaluate cells. Such asseys that my be used or variety in modificad to test immunomodulatory activity of polyspeddes of the invention include an automostic and againsts on an automostalia Acreema 4:13 Homoducular Screena 4:14. Homoducular Screena 4:14. Hymphocysts: a practical approach 4:14. Clayopt, feather of 184-6 (1995), and Robinson et al., (iii Exp. Hummol 101(3):398-407 (1959), the Monocymin of the Immunol 101(3):398-407 (1959). |
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|                                                                                                                                               | Production of RANTES in endotherial cells (sact as lumar emobilisal vein emobilisal vein (HUVEC.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                               | 283                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                               | HOUCQ17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                               | 183                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | diabetes mellitus. Additional highly preferend indication is a preferend indications in additional highly perferend indications include the preferend indications include diabetes (e.g., diabetic retinopathy, diabetic retinopathy, diabetic nephropathy, idaped disease (e.g., renal failure, rephropathy and produced and diabetic nephropathy and or other diseases and diseatedres as described in the 'Renal Disaotters' and excertible diabetic neuropathy, nerve diseases and nerve damage (e.g., due to diabetic neuropathy, hotod vessel blockage, heart disease, can the or diabetic neuropathy or blood vessel blockage, heart disease, hotod vessel blockage, heart disease, diabetic neuropathy or blood vessel blockage, actual singuists, normal blockage), actuaries, normal blockage), actuaries, normal disease, impertentically disease, general disease, affect disease, hypertension, stroke, and other diseases in preferencies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| contents of each of which are herein<br>incorporated by reference in its<br>entirety. Endothedial cells that may<br>be need according to these assess are<br>publicly available (e.g., funough the<br>ATCC <sup>19</sup> ). Exemplary endothelial<br>est list may be used according to<br>these assessy include human umbilical<br>for modifical cells (HUVEC),<br>which are endothelial cells which<br>line venous shoot vessels, and are<br>involved in functions that include,<br>but are not limited to, angiogenesis,<br>weat me profit limited to, angiogenesis,<br>acustin premeability, vasadiar roun,<br>and immune cell extravasation. | transacription through the DMEF!<br>reasonse element are well-known in the art and many be used or routinely medical to a season or contain a season or routinely medical to assess the ability of polypeptides of the invention) to activate the bMEF! response element in a reporter construct (such as that containing the GLUT4 as that containing the GLUT4 as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF! response element is present in the GLUT4 promoter and to regulate insulin production. The DMEF! response element is present in the GLUT4 promoter and motive to the 1st equived for insulin presenting in fact or the 1st equived for reason from the 1st equived for reason from the 2st equived for results in the primary insulin-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | transarption via fragilition of transarption via fragilition of transarption via fragilities of transarption via dispropersary and pre-adipocytes and pre-adipocytes fragilities of transarption via fragilities of transarption via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragilities via fragiliti |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 888                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | НРЕАДУ9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 184                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|  | modified to use for DMIFI response<br>members activities to the the theory of the<br>pre-adipocytes by polypepides of<br>pre-adipocytes by polypepides of<br>pre-adipocytes by polypepides of<br>the invention (methed assays disclosed<br>in Thai, M.V., et al., 1 Biol Chem.,<br>257237142889, 210(98); Monz, S.,<br>et al., 1 Biol Chem, 275(2)116532-8;<br>20000, Liu, M.L., et al., 1 Biol Chem,<br>20000, Liu, M.L., et al., 1 Biol Chem, 2000,<br>Arguert and a 24-base pair<br>Arguertine and 24-base pair<br>Arguertine and 24-base pair<br>Arguertine (24) 258, 128, 128, 128, 128, 128, 128, 128, 12 | assorders as extrement in con-<br>assorders, as extraction in the object, yellowing and a<br>below, yelloglemia, endocrare disorders (as described in the<br>"Induction Dodners" section below), neuropathy, vision<br>impairment (e.g. dilabelie entinopathy assort<br>would beling, and infection (e.g., infection disorders as<br>described in the "Indicators of the properties of the<br>described in the "Indicators of the<br>or of the uniony rate and skin). An<br>additional highly preferred infection<br>is obesity and o'ver oppositably<br>secondared infections actual<br>in the preferred indications and<br>preferred indications and<br>associated with insulin resistance. |
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|  | isolation. These cells undergo a pre-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|                                                       | A highly preferred indication is inguish preferred indication is a disclerate limitar. An additional highly preferred indication is a sometheria measured and an additional disclerate indication is a disclerate indication is a disclerate indication is a disclerate indication is a disclerate indication in the first methopathy in the disclerate in the first methopathy in the first methopathy in the first method in the Recall Discusses and discusders as described in the Recall Discusses and discusders as described in the Recall Discusses. In discussion in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the first in the fi |
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| under appropriate differentiation culture conditions. | Assays for the regulation of viability well-known in the art and may be well-known in the art and may be well-known in the art and may be the ability of polypedides of the mention (including artibodical sund agonists or antigonists of the polylecation of patternative solidity and polylecation of practical for a fortility and problecation of practical for a fortility and polylecation of practical for a fortility and the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present which signals the the ATP present of the sinvention of the ATP present which signals the to a fortility and managenists of the invention include the ATP present of the sinvention of (1998), Higg SM, (1927) 49(4) (1948) the contents of each of which is the contents of each of which is the cuntens of each of which is the  |
|                                                       | Regulation of vinbility and polification of pancreatio beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                       | 685                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                       | THE IBOILS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                       | 581                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                    | cells that may be used according to     | tunnel syndrome and Dupuytren's        |
|-----|---------|-----|--------------------|-----------------------------------------|----------------------------------------|
|     |         |     |                    | these assays include rat INS-1 cells.   | contracture). An additional highly     |
|     |         |     |                    | INS-1 cells are a semi-adherent cell    | preferred indication is obesity and/or |
|     |         |     |                    | line established from cells isolated    | complications associated with          |
|     |         |     |                    | from an X-ray induced rat               | obesity. Additional highly preferred   |
|     |         |     |                    | transplantable insulinoma. These        | indications include weight loss or     |
|     |         |     |                    | cells retain characteristics typical of | alternatively, weight gain. Additional |
|     |         |     |                    | native pancreatic beta cells including  | highly preferred indications are       |
|     |         |     |                    | glucose inducible insulin secretion.    | complications associated with insulin  |
|     |         |     |                    | References: Asfari et al.               | resistance.                            |
|     |         |     |                    | Endocrinology 1992 130:167.             |                                        |
|     | HPIB015 | 689 | Production of IL-6 | IL-6 FMAT. IL-6 is produced by T        | A highly preferred embodiment of       |
| 185 |         |     |                    | cells and has strong effects on B       | the invention includes a method for    |
|     |         |     |                    | cells. IL-6 participates in IL-4        | stimulating (e.g., increasing) IL-6    |
|     |         |     |                    | induced IgE production and increases    | production. An alternative highly      |
|     |         |     |                    | IgA production (IgA plays a role in     | preferred embodiment of the            |
|     |         |     |                    | mucosal immunity). IL-6 induces         | invention includes a method for        |
|     |         |     |                    | cytotoxic T cells. Deregulated          | inhibiting (e.g., reducing) IL-6       |
|     |         |     |                    | expression of IL-6 has been linked to   | production. A highly preferred         |
|     |         |     |                    | autoimmune discase, plasmacytomas,      | indication is the stimulation or       |
|     |         |     |                    | myelomas, and chronic                   | enhancement of mucosal immunity.       |
|     |         |     |                    | hyperproliferative diseases. Assays     | Highly preferred indications include   |
|     |         |     |                    | for immunomodulatory and                | blood disorders (e.g., as described    |
|     |         |     |                    | differentiation factor proteins         | below under "Immune Activity",         |
|     |         |     |                    | produced by a large variety of cells    | "Blood-Related Disorders", and/or      |
|     |         |     |                    | where the expression level is strongly  | "Cardiovascular Disorders"), and       |
|     |         |     |                    | regulated by cytokines, growth          | infection (e.g., as described below    |
|     |         |     |                    | factors, and hormones are well          | under "Infectious Disease"). Highly    |
|     |         |     |                    | known in the art and may be used or     | preferred indications include          |
|     |         |     |                    | routinely modified to assess the        | autoimmune diseases (e.g.,             |
|     |         |     |                    | ability of polypeptides of the          | rheumatoid arthritis, systemic lupus   |
|     |         |     |                    | invention (including antibodies and     | erythematosis, multiple sclerosis      |
|     |         |     |                    | agonists or antagonists of the          | and/or as described below) and         |
|     |         |     |                    | invention) to mediate                   | immunodeficiencies (e.g., as           |
|     |         |     |                    | immunomodulation and                    | described below). Highly preferred     |
|     |         |     |                    | differentiation and modulate T cell     | indications also include boosting a B  |
|     |         |     |                    | proliferation and function.             | cell-mediated immune response and      |

| alternatively suppressing a B cell-<br>mediated immune response. Highly<br>preferred indications include<br>inflammation and inflammatory | disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g.,       | myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperpoliferative Disorders"). Highty, messened indications include | neoplasms and cancers, such as,<br>myeloma, plasmacytoma, lenkemia,<br>lymphoma, melanoma, and prostate,<br>breast, lung, colon, pancreatic,<br>esophageal, stomach, brain, liver and | urnary eancer. Unter preferred indications include bening dyspooliferative disorders and pre- neoplastic conditions, such as, for example, hyperplasin, netaplasia, and/or dysplasia. Preferred indications include anemia,      | pancytopetria, leukopenia,<br>thrombocytopenia, Hodgkin's<br>disease, acute lymphocytic anemia<br>(ALL), multiple myeloma, Burkitt's<br>lymphoma, arthrifis, AIDS,<br>granulomatous disease, inflammatory<br>bowed disease, sepsis, neuropenia,   | neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocardiis, meningiis, and Lyme |
|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exemplary assays that test for immunonnodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and     | upregulation of T cell proliferation<br>and functional activities. Such<br>assays that may be used or routinely<br>modified to test immunomodulatory | and diffferentiation activity of<br>polypeptides of the invention<br>(including antibodies and agoniss or<br>anagoniss of the invention) include          | Biomolecular Screening 4:193-<br>204(1999); Rowland et al.,<br>"Lymphocytes: a practical approach"<br>Chapter 6:138-160 (2000); and<br>Verhasselt et al., J Immunol                   | 178:249-2429. Usely, the contents of each of which are berein incorporated by reference in its cutivety. Human dendritic cells that may be used according to these assessys may be isolated using techniques disclosed herein or | otherwise known in the art. Human<br>dendritic cells are angien presenting<br>cells in suspension culture, which,<br>when activated by antigen and/or<br>cytokines, initiate and upregulate T<br>cell proliferation and functional<br>activities. |                                                                                                                                                                                |
|                                                                                                                                           |                                                                                                                                                      |                                                                                                                                                           |                                                                                                                                                                                       |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                   |                                                                                                                                                                                |
|                                                                                                                                           |                                                                                                                                                      |                                                                                                                                                           |                                                                                                                                                                                       |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                   |                                                                                                                                                                                |

| HPJB33 |
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| Nessees' section below, especially of the urmin year and skin), carpul urmet synthems and Dupoyenes to contractive). An additional so contractive) An additional is obesity and/or complications associated with obesity. Additional highly preferred indications in indications indications in an Additional highly preferred alternatively, weight gain Additional highly preferred indications are complications associated with institut resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | dicheles neilins. An additional inhelp performed nicelation is a foreign experiment. An additional inhelp performed nicelation is a complication associated with a fiduces (e.g., dieducir certopopulty, idiotetic recopanyity, idiotetic recopanyity, idiotetic goods and on the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication |
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| available (e.g., through the ATCCTV) and or may be routinely generated. Exemplary paneratic of Exemplary paneratic of Exemplary paneratic of Exemplary paneratic of Exemplary paneratic of the State of Exemplary paneratic of Exemplary paneratic of Exemplary paneratic of Exemplary paneratic of Exemplary paneratic of Exemplary paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic paneratic p | Assays for measuring searchion of insulin are well-known in the art and may be used or tourniety modified to assess the ability of polypeptides of assesses the ability of polypeptides of the invention florthating unlocked and signals of the order of simulate insulin secretion. For example, Isadii secretion is measured by FMAT secretion is measured by FMAT secretion. For example, Isadii secretion from pancenic beat also by certain protein-leptides, and also by certain protein-leptides, and also by certain protein-leptides, and also by certain protein-leptides, and also by certain protein-leptides, and dishees. Excepting uses, sitem and also properpicates of the invention for inhaling secretion from pancenic (ed.) by polypeptides of the invention includes and against or anattagonists of the invention include at Frober 1 4773 NGL 970000.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HPJBK12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 681                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                         | Salapatek, A.M., et al., Mol<br>Endocrinol, 13(8):1305-17 (1999);<br>Filipsson, K., et al., Ann N Y Acad | "Cardiovascular Disorders" section<br>below), dyslipidemia, endocrine<br>disorders (as described in the |
|-----|---------|-----|-------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
|     |         |     |                         | Sci, 865:441-4 (1998); Olson, L.K.,                                                                      | "Endocrine Disorders" section                                                                           |
|     |         |     |                         | 52 (1996); and, Miraglia S et. al.,                                                                      | impairment (e.g., diabetic retinopathy                                                                  |
|     |         |     |                         | Journal of Biomolecular Screening,                                                                       | and blindness), ulcers and impaired                                                                     |
|     |         |     |                         | 4:193-204 (1999), the contents of                                                                        | wound healing, and infection (e.g.,                                                                     |
|     |         |     |                         | each of which is neven incorporated<br>by reference in its entirety.                                     | described in the "Infectious                                                                            |
|     |         |     |                         | Pancreatic cells that may be used                                                                        | Diseases" section below, especially                                                                     |
|     |         |     |                         | according to these assays are publicly                                                                   | of the urinary tract and skin), carpal                                                                  |
|     |         |     |                         | available (e.g., through the ATCCTM)                                                                     | me                                                                                                      |
|     |         |     |                         | and/or may be routinely generated.                                                                       | contracture). An additional                                                                             |
|     |         |     |                         | Exemplary pancreatic cells that may                                                                      | highly preferred indication is obesity                                                                  |
|     |         |     |                         | be used according to these assays                                                                        | and/or complications associated with                                                                    |
|     |         |     |                         | include HITT15 Cells. HITT15 are                                                                         | obesity. Additional highly preferred                                                                    |
|     |         |     |                         | an adherent epithelial cell line                                                                         | indications include weight loss or                                                                      |
|     |         |     |                         | established from Syrian hamster islet                                                                    | alternatively, weight gain. Additional                                                                  |
|     |         |     |                         | cells transformed with SV40. These                                                                       | highly preferred indications are                                                                        |
|     |         |     |                         | cells express glucagon, somatostatin,                                                                    | complications associated with insulin                                                                   |
|     |         |     |                         | and glucocorticoid receptors. The                                                                        | resistance.                                                                                             |
|     |         |     |                         | cells secrete insulin, which is                                                                          |                                                                                                         |
|     |         |     |                         | stimulated by glucose and glucagon                                                                       |                                                                                                         |
|     |         |     |                         | and suppressed by somatostatin or                                                                        |                                                                                                         |
|     |         |     |                         | glucocorticoids. ATTC# CRL-1777                                                                          |                                                                                                         |
|     |         |     |                         | Refs: Lord and Ashcroft. Biochem.                                                                        |                                                                                                         |
|     |         |     |                         | J. 219: 547-551; Santerre et al. Proc.                                                                   |                                                                                                         |
|     |         |     |                         | Natl. Acad. Sci. USA 78: 4339-4343,                                                                      |                                                                                                         |
|     |         |     |                         | 1981.                                                                                                    |                                                                                                         |
|     | HPJBK12 | 165 | Regulation of apoptosis | Caspase Apoptosis. Assays for                                                                            | Preferred embodiments of the                                                                            |
| 187 |         |     | of immune cells (such   | caspase apoptosis are well known in                                                                      | invention include using polypeptides                                                                    |
|     |         |     | as mast cells).         | the art and may be used or routinely                                                                     | of the invention (or antibodies,                                                                        |
|     |         |     |                         | modified to assess the ability of                                                                        | agonists, or antagonists thereof) in                                                                    |
|     |         |     |                         | polypeptides of the invention                                                                            | detection, diagnosis, prevention,                                                                       |
|     |         |     |                         | (including antibodies and agonists or                                                                    | and/or treatment of asthma, allergy,                                                                    |
|     |         |     |                         | antagonists of the invention) to                                                                         | hypersensitivity and inflammation.                                                                      |

| regulate caspase protease-mediated | apoptosis in immune cells (such as, | for example, in mast cells). Mast | cells are found in connective and | mucosal tissues throughout the body, | and their activation via | immunoglobulin E -antigen, | promoted by T helper cell type 2 | cytokines, is an important component | of allergic disease. Dysregulation of | mast cell apoptosis may play a role in | allergic disease and mast cell tumor | survival. Exemplary assays for | caspase apoptosis that may be used | or routinely modified to test capase | apoptosis activity induced by | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in: Masuda A, et | al., J Biol Chem, 276(28):26107- | 26113 (2001); Yeatman CF 2nd, et | al., J Exp Med, 192(8):1093-1103 | (2000);Lee et al., FEBS Lett 485(2- | 3): 122-126 (2000); Nor et al., J Vasc | Res 37(3): 209-218 (2000); and | Karsan and Harlan, J Atheroscler | Thromb 3(2): 75-80 (1996); the | contents of each of which are herein | incorporated by reference in its | entirety. Immune cells that may be | used according to these assays are | publicly available (e.g., through | commercial sources). Exemplary | immune cells that may be used | according to these assays include | mast cells such as the HMC human |
|------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|--------------------------|----------------------------|----------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------|------------------------------------|--------------------------------------|-------------------------------|-------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|----------------------------------|----------------------------------|----------------------------------|-------------------------------------|----------------------------------------|--------------------------------|----------------------------------|--------------------------------|--------------------------------------|----------------------------------|------------------------------------|------------------------------------|-----------------------------------|--------------------------------|-------------------------------|-----------------------------------|----------------------------------|
|                                    |                                     |                                   |                                   |                                      |                          |                            |                                  |                                      |                                       |                                        |                                      |                                |                                    |                                      |                               |                               |                                       |                                       |                                       |                                  |                                  |                                  |                                     |                                        |                                |                                  |                                |                                      |                                  |                                    |                                    |                                   |                                |                               |                                   |                                  |
|                                    |                                     |                                   |                                   |                                      |                          |                            |                                  |                                      |                                       |                                        |                                      |                                |                                    |                                      |                               |                               |                                       |                                       |                                       |                                  |                                  |                                  |                                     |                                        |                                |                                  |                                |                                      |                                  |                                    |                                    |                                   |                                |                               |                                   | _                                |

|                 | A raginy presence entonation on the investment entonation of an amendation includes a method from including a method from thinking methodism is entonation includes a method for inhibiting endothelial cell growth. A highly preferred emodeliated to the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the investment of the original of a condecident of the investment of the original originates of the investment of the original originates of the investment of the original originates of the investment of the original originates of the extra originates of the investment of the original originates of the original originates of the original originates of the original originates of the original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original original o |
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| mast cell line. | names assay, The man pay a mass-<br>sassiys for signal transduction that<br>or gappiosis are well Known in the and<br>rappiosis are well Known in the and<br>marphy and the invention) to<br>modified to assass the ability of<br>modified to assass the ability of<br>modified to assass the ability of<br>promote or rithidis cell proliferation, to<br>promote or rithidis cell proliferation, to<br>promote or rithidis cell proliferation, to<br>promote or rithidis cell proliferation, assays for DKK and p38 kinase-<br>ardivity that may be used or routinely<br>modified to test JMK and p38 kinase-<br>tarity that may be used or routinely<br>modified to test JMK and p38 kinase-<br>tal agoinst or relangenists of the<br>invention include the usages, of the<br>invention include the usages, of the<br>invention include the usages of the<br>invention include the usages of the<br>invention include the usages of the<br>invention (nebuling unbeddes of<br>the contents of the course of the theory include<br>the contents of test of which are<br>the contents of test of which are<br>the contents of test of which are<br>the sassus are publicly available (e.g.,<br>human turnsliked win redothedial cells that<br>human turnsliked weit redothedial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                 | Terdotherial Cell p38 or<br>InK Signaling<br>Pathway.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| _               | 160                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                 | 187                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| inter venous embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred s, vascular embodiment of the invention includes a method for reducing cardiac hypertrophy. An attentive | highly preferred embediment of the investion includes a method for investion includes a method for inducting cardiae hypertrophy.  Highly proferred infections include non-plastic diseases (e.g., as described non-plastic diseases) (e.g., as described non-plastic diseases) (e.g., as described non-plastic diseases), and disearches of the cardiovasculae ystem (e.g., heart diseases, congestive heart failure, hypertension, and its entrollar diseases, congestive heart failure, hypertension, and its ventricular objection on the ventral and admenselymoral, virtual disease, dishorts on popularly, intraordial shunt, cardiae hypertrophy, intraordiae shunt, cardiae hypertrophy. | execrIved below mades—smooth<br>"Cardiowasum Disorders"). Highly<br>preferred indications include<br>cardiowasum fact voidoletial and or<br>angiogenei disorders (e.g., systemic<br>disorders that after vessels such as<br>diabetes mellina, as well as diseases<br>of the vessels inclusively, such and or<br>the versels increased, as the such as<br>indications that simulate<br>angiogeneis as and or<br>cardiowasularization. Highly<br>cardiowasularization Highly |
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| endothelial cells swheb line evonous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular income, and immune cell extravassation.       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| preferred are indications that inhibit | cardiovascularization. Highly | preferred indications include | antiangiogenic activity to treat solid | tumors, leukemias, and Kaposi"s | sarcoma, and retinal disorders. | Highly preferred indications include | neoplasms and cancer, such as, | Kaposi"s sarcoma, hemangioma | (capillary and cavernous), glomus | tumors, telangiectasia, bacillary | angiomatosis, | hemangioendothelioma, | angiosarcoma, | haemangiopericytoma, | lymphangioma, lymphangiosarcoma. | Highly preferred indications also | include cancers such as, prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver, | and urinary cancer. Preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | and/or dysplasia. Highly | preferred indications also include | arterial disease, such as, | atherosclerosis, hypertension, | coronary artery disease, | inflammatory vasculitides, | Reynaud's disease and Reynaud's | phenomenom, aneurysms, restenosis; | venous and lymphatic disorders such |  |
|----------------------------------------|-------------------------------|-------------------------------|----------------------------------------|---------------------------------|---------------------------------|--------------------------------------|--------------------------------|------------------------------|-----------------------------------|-----------------------------------|---------------|-----------------------|---------------|----------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|------------------------------------|-------------------------------|----------------------------|-------------------------------------|-------------------------------------|--------------------------|------------------------------------|----------------------------|--------------------------------|--------------------------|----------------------------|---------------------------------|------------------------------------|-------------------------------------|--|
| _                                      |                               |                               |                                        |                                 |                                 |                                      |                                |                              |                                   |                                   |               |                       |               |                      |                                  |                                   |                                    |                                  |                                    |                               |                            |                                     |                                     |                          |                                    |                            |                                |                          |                            |                                 |                                    |                                     |  |

| disorders such as peri<br>disease, and cancer.                  | disorders such as peripheral vascular<br>disease, and cancer. Highly          |
|-----------------------------------------------------------------|-------------------------------------------------------------------------------|
| preferred indicati                                              | preferred indications also include                                            |
| trauma such as w<br>injured tissue (e.s                         | trauma such as wounds, burns, and<br>injured tissue (e.g., vascular injury    |
| such as, injury re                                              | such as, injury resulting from balloon                                        |
| angioplasiy, and lesions), implant                              | angioplasty, and atheroschlerotic<br>lesions), implant fixation, scarring,    |
| ischemia reperfusion injury,                                    | usion injury,                                                                 |
| rheumatoid arthri<br>disease renal dis                          | rheumatoid arthritis, cerebrovascular<br>disease renal diseases such as acute |
| renal failure, and osteoporosis.                                | d osteoporosis.                                                               |
| Additional highly preferred                                     | ly preferred                                                                  |
| indications include stroke, graft                               | ude stroke, graft                                                             |
| rejection, diagence or other retinopathies thrombotic and       | ue or outer                                                                   |
| coagulative disor                                               | coagulative disorders, vascularitis,                                          |
| lymph angiogenesis, sexual                                      | resis, sexual                                                                 |
| disorders, age-related macular                                  | elated macular                                                                |
| degeneration, and treatment                                     | nd treatment                                                                  |
| /prevention of en                                               | prevention of endometriosis and                                               |
| related condition                                               | related conditions. Additional highly                                         |
| preferred indications include                                   | thons include                                                                 |
| Indiomas, heart disease, cardiac arrest heart valve disease and | disease, cardiac                                                              |
| vascular disease.                                               | e. Preferred                                                                  |
| indications inclu                                               | indications include blood disorders                                           |
| (e.g., as described below under                                 | ed below under                                                                |
| "Immune Activit                                                 | "Immune Activity", "Blood-Related                                             |
| Disorders", and/c                                               | Disorders", and/or "Cardiovascular                                            |
| Disorders"). Pre-                                               | Disorders"). Preferred indications                                            |
| include autoimm                                                 | include autoimmune diseases (e.g.,                                            |
| rheumatoid arthri                                               | rheumatoid arthritis, systemic lupus                                          |
| erythematosis, m                                                | erythematosis, multiple sclerosis                                             |
| and/or as described below) and                                  | bed below) and                                                                |
| immunodeficiencies (e.g., as                                    | ncies (e.g., as                                                               |
| described below). Additional                                    | v). Additional                                                                |

| preferred indications include inflammatory and inflammatory disorders (such as acute and chronic inflammatory (diseases, e.g., inflammatory boved diseases Cobrib of diseases), and pain management. | lar lar lar lar lar lar lar lar lar lar                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                      | Activation of Kinnes assays, for example an El-L kinnes assay, for ell politerentiation of differentiation of the area man may assay of the shifting of polyperplaces of the assay of a rounding anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius anthodius and agonis anthodius |
|                                                                                                                                                                                                      | HPICL22 592                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                      | 88                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                      | _                                   |                                      | _                                           | _                                 | _                                   |                                    |                                    | _                                      |                                     |                                      |                                     | _                            |                                     | _                                   | _                            | _                                | _                                |                                  |                              | _                                     |                                      |                                   | _                                      |                                    |                                      |                                |                                     | _                                     |                                 |                                     | _                           | _                                 | _                                |                                     | _                         | _                                    |
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| "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel      | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, |
| entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ). Exemplary | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |
|                                      |                                     |                                      |                                             |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |
|                                      |                                     |                                      |                                             |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     | _                            | _                                | _                                |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             | _                                 |                                  |                                     |                           |                                      |
|                                      |                                     |                                      |                                             |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |

| _ |  | stroke and other diseases and           |
|---|--|-----------------------------------------|
|   |  | disorders to described in the           |
|   |  | disolucis as described in the           |
|   |  | "Cardiovascular Disorders" section      |
|   |  | below), dyslipidemia, endocrine         |
|   |  | disorders (as described in the          |
|   |  | "Endocrine Disorders" section           |
|   |  | below), neuropathy, vision              |
|   |  | impairment (e.g., diabetic retinopathy  |
|   |  | and blindness), ulcers and impaired     |
|   |  | wound healing, infection (e.g.,         |
|   |  | infectious diseases and disorders as    |
|   |  | described in the "Infectious            |
|   |  | Diseases" section below (particularly   |
|   |  | of the urinary tract and skin). An      |
|   |  | additional highly preferred indication  |
|   |  | is obesity and/or complications         |
|   |  | associated with obesity. Additional     |
|   |  | highly preferred indications include    |
|   |  | weight loss or alternatively, weight    |
|   |  | gain. Additional highly                 |
|   |  | preferred indications are               |
|   |  | complications associated with insulin   |
|   |  | resistance. Additional highly           |
|   |  | preferred indications are disorders of  |
|   |  | the musculoskeletal systems             |
|   |  | including myopathies, muscular          |
|   |  | Š                                       |
|   |  | herein. Additional highly               |
|   |  | preferred indications include,          |
|   |  | hypertension, coronary artery           |
|   |  | disease, dyslipidemia, gallstones,      |
|   |  | osteoarthritis, degenerative arthritis, |
|   |  | eating disorders, fibrosis, cachexia,   |
|   |  | and kidney diseases or disorders.       |
|   |  | Preferred indications include           |
|   |  | neoplasms and cancer, such as,          |
|   |  | lymphoma, leukemia and breast,          |

| colon, and kidney cancer. Additional appetred indications include melanorus, prostate, Jung metaverati, cespoingeal, stomes, brain, liver, and trimary cancer. Including preferred indications include lipomas and liposarcomas. Other preferred indications include benign deposition of propositions include benign copplisation conditions, such as, for exposition for admitted benigns and conditions, such as, for example, hyporphista, metaphistia, and chysikistia. | diabetes mellins.  A highly predured indication is diabetes mellins.  Standard highly performed indication is a complication associated with diabetes (e.g., diabetes (e.g., diabetes refused with diabetes (e.g., diabetes refused with diabetes (e.g., diabetes refused with diabetes et al., diabetes refused with diabetes et al., diabetes regulated with diabetes et al., diabetes regulated as a diabete expension of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company o |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | stassys for measuring estaining that are well-known in the art and may be add or routinely notified to assess the shilty of polygopides of the selection of the control (including authorities and agontists or antagonists of the mirroration) to mobilize estainm. For example, the FLPR assay may be used to measure influx or cleation. Use the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of calcium. Extracellular estainm is the control of calcium, Federal and finders or an antibut of calcium, proposed and alterations in cell fundrious. Exemplary assays that may be used or routinely undired on polypopides of the invention included manages disclosed in Saint S. et al., Enderringon; 15(11), 5(2), 5(2), 5(2), 5(3), 5(3), 5(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4), 7(4),  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Stimulation of Calcium<br>Fluxin pancreatic beta<br>cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 593                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | IPMDK28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 88                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| registrates (sectored in the decidence) sectored in the "Tachdorine Disorders" section blooders" section impairment (s. disorders) and impairment (s. disorders) and impairment (s. disorders) and hindress), there and impairment (s. disorders) and hindress), there and impairment (s. disorders) and infections disorders and the interest and single secret for the unimary treat and single secret and single secret for the unimary treat and single secret for the unimary treat and single secret and single secret for the unimary treatment and pulpayers is the unimed syndrome and sometiment as and secret for all treatment and the unimary secret for all treatments are completely registered.  In an                                                                                                                              | 1 A highly prefered indication is indichese mellins. Additional lightly no in preferred indications include rockly complications sectioned with dislatence (e.g., diabetic rechinopathy, dated greaters of e.g., remail failure, inchropathy and and an additional properties of e.g., remail failure, inchropathy and and and a failure, inchropathy and and an addition that the mellins in the "Renal Disorders" described in the "Renal Disorders". |
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| Indocrinology, 184(7):280-6. Indocrinology, 184(7):280-6. Bischem, 1384 (P. 18):487-11. Bischem, 1384 (P. 18):487-11. Bischem, 1384 (P. 18):487-11. Calcium 1898 (Work) executed (Calcium 1898) who because of the Calcium 1898 (Work) executed (1989). In eventuents of each of Workhold (1989), the connents of each of Workhold (1989), the used and force of publicly available (e.g., Innogal the used conding to these subsystem than beat exactling to these subsystem of the each exception of the season in the each exception. The est except in some exception. The est secrete in antility which is simulated by glucoscitosid exception. The est except in sufficient of all the connection of the exception. The est secrete in antility which is simulated by glucoscitosid exception. The Calc secrete in antility which is simulated by glucoscitosid exception. The Exception of Euchem 1.2 19; 547-551; 18, 18, 18, 18, 18, 18, 18, 18, 18, 18, | Assays for the regulation of transcription through the DMET response element are well-known in the art and may be treed or notatively modified to assess the ability of modified to assess the ability of pulyppiduse of the tiventom (including antipodies and agoniss or anatomists of the invention) advive the DMET resconse                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Regulation of transcription via transcription via DMHFI response element in adipocytes and pre-adipocytes                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 594                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HPRAL78                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 190                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| section below) diabetic neuronathy    | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental      | confusion, drowsiness, nonketotic     | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,     | microvascular disease, hypertension,  | stroke, and other diseases and      | disorders as described in the | "Cardiovascular Disorders" section  | below), dyslipidemia, endocrine     | disorders (as described in the     | "Endocrine Disorders" section       | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious      | Diseases" section below, especially | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications    | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly preferred | indications are complications  | associated with insulin resistance. |                                     |                                  |                               |
|---------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|----------------------------------|---------------------------------------|----------------------------------|-------------------------------------|-------------------------------|---------------------------------------|-------------------------------------|-------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|----------------------------------------|------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------|
| element in a remorter construct (such | as that containing the GLUT4   | promoter) and to regulate insulin   | production. The DMEF1 response        | element is present in the GLUT4 | promoter and binds to MEF2          | transcription factor and another | transcription factor that is required | for insulin regulation of Glut4  | expression in skeletal muscle.      | GLUT4 is the primary insulin- | responsive glucose transporter in fat | and muscle tissue. Exemplary assays | that may be used or routinely | modified to test for DMEF1 response | element activity (in adipocytes and | pre-adipocytes) by polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed    | inThai, M.V., et al., J Biol Chem,  | 273(23):14285-92 (1998); Mora, S.,  | et al., J Biol Chem, 275(21):16323-8 | (2000); Liu, M.L., et al., J Biol | Chem, 269(45):28514-21 (1994);      | "Identification of a 30-base pair  | regulatory element and novel DNA       | binding protein that regulates the | human GLUT4 promoter in             | transgenic mice", J Biol Chem. 2000  | Aug 4;275(31):23666-73; Berger, et   | al., Gene 66:1-10 (1988); and,    | Cullen, B., et al., Methods in | Enzymol. 216:362-368 (1992), the    | contents of each of which is herein | incorporated by reference in its | entirety. Adipocytes and pre- |
|                                       |                                |                                     |                                       |                                 |                                     |                                  |                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |
| -                                     |                                |                                     |                                       |                                 |                                     |                                  |                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | disheres mellitus. An additional indication is a diship preferred indication is a diship preferred indication is a complication associated with complication associated with complication associated with calculation of the complication associated with cidabetic retinopathy, ickiney disease (e.g., trend influte, rephropathy ickiney diseases (e.g., trend influte, rephropathy and cooled the companies and diseases and diseases and diseases and disease and ancre diamage (e.g., trend influter, nearrow diseases and narve diamage (e.g., due to disease the ancre diamage of control disease and nerve diamage of control short in the companies, and the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the contr |
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| adipocytes that may be tused according to these assays are publicly available (e.g., through the ATCCP). The according to these assays are publicly according to these assays include the Exemplary cells that may be used according to these assays include the mouse 3T3-LL cells turn a deherent mause preadpocyte cell fine whose 3T3-LL cells are a continuous substant of 3T3 in fibroblass developed through cloud isolation. These cells undergo a preadpocyte on adipocyte on darboe-like conversion and fibroblass developed through cloud isolation. These cells undergo a preadpocyte on adipocyte on adipocyte on adipocyte on adipocyte on edipocyte on adipocyte on edipocyte on entered and edificientiation culture conditions. | stayes for measuring secucion of insulin are well-known in the art and may be used or troutinely modified to assess the ability of polycyptides of the invention (including ambidies and agoniss or matgoniss or fine secucion. For example, insulin secucion is or example, insulin secucion is or example, insulin secucion for example, insulin secucion for on part of the first of the properties and the properties of the integrated by the properties and the properties of the integrated by the properties, and also by certain proteins/peptides, and also by certain proteins/peptides, and dichedes. Exemplery seasys fain may be tased or routinely modified to test of routinely modified to the insulination of finantia secucion (from pancreatic cells) by the mytholic and agoniss or distribution includes and agoniss or distribution includes ansats disclosed in: Shimital, H., et asserts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Insulin Screttion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 595                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HRABASO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 161                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| andothalial call amounth A hindyly  | Ξ                                   | invention includes a method for | stimulating endothelial cell          | proliferation. An alternative highly | preferred embodiment of the           | invention includes a method for      | inhibiting endothelial cell       | proliferation. A highly    | preferred embodiment of the   | invention includes a method for       | stimulating apoptosis of endothelial  | cells. An alternative highly preferred | embodiment of the invention  | includes a method for inhibiting (e.g., | decreasing) apoptosis of endothelial | cells. A highly preferred  | embodiment of the invention      | includes a method for stimulating | (e.g., increasing) endothelial cell | activation. An alternative highly | preferred embodiment of the       | invention includes a method for     | inhibiting the activation of (e.g.,  | r ina                          | endothelial cells. A highly          | preferred embodiment of the    | invention includes a method for    | stimulating endothelial cell      | differentiation. An alternative highly | preferred embodiment of the | invention includes a method for     | inhibiting endothelial cell        | differentiation. A highly           | preferred embodiment of the        | invention includes a method for  | stimulating angiogenisis. An |
|-------------------------------------|-------------------------------------|---------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------|-------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|------------------------------|-----------------------------------------|--------------------------------------|----------------------------|----------------------------------|-----------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|-------------------------------------|--------------------------------------|--------------------------------|--------------------------------------|--------------------------------|------------------------------------|-----------------------------------|----------------------------------------|-----------------------------|-------------------------------------|------------------------------------|-------------------------------------|------------------------------------|----------------------------------|------------------------------|
| the skilling of notamentides of the | invention (including antibodies and | agonists or antagonists of the  | invention) to promote or inhibit cell | proliferation, activation, and       | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110 | (1998); Berra et al., Biochem           | Pharmacol 60(8):1171-1178 (2000);    | Gupta et al., Exp Cell Res | 247(2):495-504 (1999); Chang and | Karin, Nature 410(6824):37-40     | (2001); and Cobb MH, Prog Biophys   | Mol Biol 71(3-4):479-500 (1999);  | the contents of each of which are | herein incorporated by reference in | its entirety. Endothelial cells that | may be used according to these | assays are publicly available (e.g., | through the ATCCTM). Exemplary | endothelial cells that may be used | according to these assays include | human umbilical vein endothelial       | cells (HUVEC), which are    | endothelial cells which line venous | blood vessels, and are involved in | functions that include, but are not | limited to, angiogenesis, vascular | permeability, vascular tone, and | immune cell extravasation,   |
|                                     |                                     |                                 |                                       |                                      |                                       |                                      |                                   |                            |                               |                                       |                                       |                                        |                              |                                         |                                      |                            |                                  |                                   |                                     |                                   |                                   |                                     |                                      |                                |                                      |                                |                                    |                                   |                                        |                             |                                     |                                    |                                     |                                    |                                  |                              |
|                                     |                                     |                                 |                                       |                                      |                                       |                                      |                                   |                            |                               |                                       |                                       |                                        |                              |                                         |                                      |                            |                                  |                                   |                                     |                                   |                                   |                                     |                                      |                                |                                      |                                |                                    |                                   |                                        |                             |                                     |                                    |                                     |                                    |                                  | _                            |

|  | alternative highly preferred                                        |
|--|---------------------------------------------------------------------|
|  | includes a method for inhibiting                                    |
|  | angiogenesis. A highly                                              |
|  | preferred embodiment of the                                         |
|  | invention includes a method for<br>reducing cardiac hypertrophy. An |
|  | alternative highly preferred                                        |
|  | embodiment of the invention                                         |
|  |                                                                     |
|  | cardiac hypertrophy. Highly                                         |
|  | preferred indications include                                       |
|  | neoplastic diseases (e.g., as described                             |
|  | below under "Hyperproliferative                                     |
|  | Disorders"), and disorders of the                                   |
|  | cardiovascular system (e.g., heart                                  |
|  | disease, congestive heart failure,                                  |
|  | hypertension, aortic stenosis,                                      |
|  | cardiomyopathy, valvular                                            |
|  | regurgitation, left ventricular                                     |
|  | dysfunction, atherosclerosis and                                    |
|  | atherosclerotic vascular disease,                                   |
|  | diabetic nephropathy, intracardiac                                  |
|  | shunt, cardiac hypertrophy,                                         |
|  | myocardial infarction, chronic                                      |
|  | hemodynamic overload, and/or as                                     |
|  | described below under                                               |
|  | "Cardiovascular Disorders"). Highly                                 |
|  | preferred indications include                                       |
|  | cardiovascular, endothelial and/or                                  |
|  | angiogenic disorders (e.g., systemic                                |
|  | disorders that affect vessels such as                               |
|  | diabetes mellitus, as well as diseases                              |
|  | of the vessels themselves, such as of                               |
|  | the arteries, capillaries, veins and/or                             |
|  | lymphatics). Highly preferred are                                   |
|  | indications that stimulate                                          |

|  |   | anciogenesis and/or                    |
|--|---|----------------------------------------|
|  |   | cardiovascularization. Highly          |
|  |   | preferred are indications that inhibit |
|  |   | angiogenesis and/or                    |
|  |   | cardiovascularization. Highly          |
|  |   | preferred indications include          |
|  |   | antiangiogenic activity to treat solid |
|  | _ | tumors, leukemias, and Kaposi"s        |
|  | - | sarcoma, and retinal disorders.        |
|  |   | Highly preferred indications include   |
|  | _ | neoplasms and cancer, such as,         |
|  |   | Kaposi"s sarcoma, hemangioma           |
|  | _ | (capillary and cavernous), glomus      |
|  | _ | tumors, telangiectasia, bacillary      |
|  |   | angiomatosis,                          |
|  | _ | hemangioendothelioma,                  |
|  | - | angiosarcoma,                          |
|  | _ | haemangiopericytoma,                   |
|  | _ | lymphangioma, lymphangiosarcoma.       |
|  | _ | Highly preferred indications also      |
|  | _ | include cancers such as, prostate,     |
|  | _ | breast, lung, colon, pancreatic,       |
|  | _ | esophageal, stomach, brain, liver,     |
|  |   | and urinary cancer. Preferred          |
|  |   | indications include benign             |
|  | _ | dysproliferative disorders and pre-    |
|  | _ | neoplastic conditions, such as, for    |
|  |   |                                        |
|  |   | and/or dysplasia. Highly               |
|  |   | preferred indications also include     |
|  |   | arterial disease, such as,             |
|  | - | atherosclerosis, hypertension,         |
|  |   | coronary artery disease,               |
|  |   | inflammatory vasculitides,             |
|  | _ | Reynaud"s disease and Reynaud"s        |
|  | _ | phenomenom, aneurysms, restenosis;     |
|  |   | venous and lymphatic disorders such    |

|  |   | as thrombophlebitis, lymphangitis,     |
|--|---|----------------------------------------|
|  |   | and lymphedema; and other vascular     |
|  |   | disorders such as peripheral vascular  |
|  |   | disease, and cancer. Highly            |
|  | _ | preferred indications also include     |
|  | _ | trauma such as wounds, burns, and      |
|  |   | injured tissue (e.g., vascular injury  |
|  |   | such as, injury resulting from balloon |
|  |   | angioplasty, and atheroschlerotic      |
|  |   | lesions), implant fixation, scarring,  |
|  |   | ischemia reperfusion injury,           |
|  |   | rheumatoid arthritis, cerebrovascular  |
|  |   | disease, renal diseases such as acute  |
|  | _ | renal failure, and osteoporosis.       |
|  |   | Additional highly preferred            |
|  |   | indications include stroke, graft      |
|  | _ | rejection, diabetic or other           |
|  | _ | retinopathies, thrombotic and          |
|  |   | coagulative disorders, vascularitis,   |
|  |   | lymph angiogenesis, sexual             |
|  |   | disorders, age-related macular         |
|  |   | degeneration, and treatment            |
|  | _ | /prevention of endometriosis and       |
|  |   | related conditions. Additional highly  |
|  | _ | preferred indications include          |
|  |   | fibromas, heart disease, cardiac       |
|  |   | dis                                    |
|  |   | vascular disease. Preferred            |
|  |   | indications include blood disorders    |
|  | _ | (e.g., as described below under        |
|  | _ | "Immune Activity", "Blood-Related      |
|  | _ | Disorders", and/or "Cardiovascular     |
|  |   | Disorders"). Preferred indications     |
|  |   | include autoimmune diseases (e.g.,     |
|  |   | rheumatoid arthritis, systemic lupus   |
|  | _ | erythematosis, multiple sclerosis      |
|  |   | and/or as described below) and         |

|     |         |     |                         | JINK and pas kinase activity that may         | rneumatoid artnritis, systemic lupus   |
|-----|---------|-----|-------------------------|-----------------------------------------------|----------------------------------------|
|     |         |     |                         | be used or routinely modified to test         | erythematosis, multiple sclerosis      |
|     |         |     |                         | JNK and p38 kinase-induced activity           | and/or as described below) and         |
|     |         |     |                         | of polypeptides of the invention              | immunodeficiencies (e.g., as           |
|     |         |     |                         | (including antibodies and agonists or         | described below). Additional highly    |
|     |         |     |                         | antagonists of the invention) include         | preferred indications include          |
|     |         |     |                         | the assays disclosed in Forrer et al.,        | inflammation and inflammatory          |
|     |         |     |                         | Biol Chem 379(8-9):1101-1110                  | disorders. Highly preferred            |
|     |         |     |                         | (1998); Gupta et al., Exp Cell Res            | indications also include neoplastic    |
|     |         |     |                         | 247(2): 495-504 (1999); Kyriakis              | diseases (e.g., leukemia, lymphoma,    |
|     |         |     |                         | JM, Biochem Soc Symp 64:29-48                 | and/or as described below under        |
|     |         |     |                         | (1999); Chang and Karin, Nature               | "Hyperproliferative Disorders").       |
|     |         |     |                         | 410(6824):37-40 (2001); and Cobb              | Highly preferred indications include   |
|     |         |     |                         | MH, Prog Biophys Mol Biol 71(3-               | neoplasms and cancers, such as,        |
|     |         |     |                         | 4):479-500 (1999); the contents of            | leukemia, lymphoma, prostate,          |
|     |         |     |                         | each of which are herein                      | breast, lung, colon, pancreatic,       |
|     |         |     |                         | incorporated by reference in its              | esophageal, stomach, brain, liver,     |
|     |         |     |                         | entirety. T cells that may be used            | and urinary cancer. Other preferred    |
|     |         |     |                         | according to these assays are publicly        | indications include benign             |
|     |         |     |                         | available (e.g., through the                  | dysproliferative disorders and pre-    |
|     |         |     |                         | ATCC <sup>TM</sup> ). Exemplary mouse T cells | neoplastic conditions, such as, for    |
|     |         |     |                         | that may be used according to these           | example, hyperplasia, metaplasia,      |
|     |         |     |                         | assays include the CTLL cell line,            | and/or dysplasia. Preferred            |
|     |         |     |                         | which is an IL-2 dependent                    | indications include arthritis, asthma, |
|     |         |     |                         | suspension-culture cell line with             | AIDS, allergy, anemia, pancytopenia,   |
|     |         |     |                         | cytotoxic activity.                           | leukopenia, thrombocytopenia,          |
|     |         |     |                         |                                               | Hodgkin"s disease, acute               |
|     |         |     |                         |                                               | lymphocytic anemia (ALL),              |
|     |         |     |                         |                                               | plasmacytomas, multiple myeloma,       |
|     |         |     |                         |                                               | Burkitt's lymphoma, granulomatous      |
|     |         |     |                         |                                               | disease, inflammatory bowel disease,   |
|     |         |     |                         |                                               | sepsis, psoriasis, suppression of      |
|     |         |     |                         |                                               | immune reactions to transplanted       |
|     |         |     |                         |                                               | organs and tissues, endocarditis,      |
|     |         |     |                         |                                               | meningitis, and Lyme Disease.          |
|     | HRACD15 | 969 | Regulation of apoptosis | Caspase Apoptosis. Assays for                 | Preferred embodiments of the           |
| 192 |         |     | of immune cells (such   | caspase apoptosis are well known in           | invention include using polypeptides   |

| of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of salma, allergy, hypersensitivity and inflammation. |                                                                                                                                                                    |                                                                                                                                                                                                                                   |                                                                                                                                                                    |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antigonists of the meeting).        | apoptosis in immune cells (such as, for example, in mast cells. Mast cells are found in connective and mucosal usacse flroughout the body and their activation via | infinitiogotomic variages,<br>promoted by T helper cell type 2<br>cytokines, is an important component<br>of allergic disease. Dysregulation of<br>mast cell apoptosis may play a role in<br>allergic disease and mast cell tumor | survival. Exemplary assays for caspase apoptosis that may be used or routinely modified to test capase apoptosis activity induced by polypeptides of the invention | (including antibodies and agonists or<br>antagonists of the invention) include<br>the assays disclosed in: Masuda A, et<br>al., J Biol Chen, 276(29):26 (107<br>26 i 15 (2001); Yeatman CP Zud, et<br>al., J Exp. Med. 192(2):1093-1103 | 3): 122-126 (2000); Nor et al., J Visse<br>Res 37(3): 20-2128 (2000); and<br>Karsun and Haffan, J Atheroseler<br>Thromp 3(2): 75-80 (1996); the<br>contents of each of which are herein<br>incorporated by reference in its<br>entirey. Immune cells that may be<br>used according to these assays are |
| as mast cells).                                                                                                                                                                |                                                                                                                                                                    |                                                                                                                                                                                                                                   |                                                                                                                                                                    |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                |                                                                                                                                                                    |                                                                                                                                                                                                                                   |                                                                                                                                                                    |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                        |

| HRACJ35 |     |     |                                                                         | commercial sources). Exemplary immune cells that may be used according to these assays include mast cells such as the HMC human mast cells line.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------|-----|-----|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | 135 | 765 | Regulation of Factories and Engine in hepatocytes Engine in hepatocytes | remarging to Ababic Elevane and well-known in the art and may be used to routinely no modified to assess the ability of polypeptides of the ability of polypeptides of the ability of polypeptides of the ability of polypeptides of the ability of polypeptides of the agencies of the arteriof in Cheduler amanging ambodies and agonists or amagonists of the Malic Enzyme is proposeries, the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of the ability of a the ability of the ability of a transcriptor. | A highly preferred indication is additional highly preferred indication and additional highly preferred indication the additional highly preferred indication that the additional highly preferred indication that the additional highly preferred indication that the additional highly additional highly additional additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional highly additional and highly vision highly vision below). Additional pilonder's section below), and highly significant and company of the distriction and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significant and company and highly significa |

| infections diseases and disorders as searched in the "Infections Progressia" search of the "Infections of the union year and shah, carpal turned syndrome and Dupptyrent's contracture). An additional highly preferred indication is obesity and complications associated with obesity. Additional highly preferred indications include vieght loss or alternatively, weight gain.  In the progressian of the preferred indications include vieght loss or alternatively, weight gain.  In the progressian of the preferred indications include vieght loss or alternatively, weight gain.  In the progressian of the preferred indications include vieght loss or alternatively weight gain.                                                                                                                                                         | highly preferred indications include inflammation (acute and cironic).  The acute of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control |
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| 1 [Jipcuberg, A., et al., J Biol Chem., 12(2):22(2)(20(2)) (2(2)); Berger, et al., Gene 66:1-10 (1988); Berger, et al., Mednos in Enzymel. 216:542:548 (1992), Incentive J. Generoles of even of which is herein morporated by reference in its morporated by reference in its useful continuity. Hepotocytes that may be used according to these assays are bringled by the seed according to these assays inchingles the mouse 3T3-L1 cell line. 3T3-L1 is a mouse 3T3-L1 cell line. 3T3-L1 is a mouse 3T3-L1 cell line. 3T3-L1 is a mouse says inchingles the mouse 3T3-L1 cell line. 3T3-L1 is a mouse are substantial of 3T3 incheblass developed through clonal influences and proceditions. | Assays for measuring expression of VCAM are well-known in the art and may be used or notwitted pradicified to assess the ability of polyperdess of the invention (including antipodics and agonists or antiquing such or for invention) to regulate VCAM in the proposition. For example, PMAT may be used to meature the PMAT may be used to meature the organisation of cell surface VCAM-1 corpression in endothelial cells are ucells that line objects, and are involved in mindention that induction that induc |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | by Abustion of VCAM in endotheial cells calls is human imbilical vein cedotheial cells (HUVEC))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 597                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HRACJ35                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| cancers such as, for example, the determing Jupungan and prostate, breast lang colonia, medianous, renal cell carcinous, and prostate, breast, lang, colony, pameratic, esophageal, stomach, praint iver and unitary cancer. Other preferred unitary cancer. Other preferred unitary cancer. Other preferred dysponliterative disorders and prevailed to obsensite conditions, such as, for example, hyporplasia, metaplissia, and or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | A highly preferred indication is diabetes mellins.  A highly perferred indication is a dominant play perferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, thirty disease (e.g., retal fallure, hephropathy and work or the diseases and diseases and diseases as a diseases and diseases and diseases and diseases and diseases and interve diseases and interve diseases and interve diseases and interve diseases and interve diseases and interve diseases, are the object in emposity, he hood vessel blockeg, hear disease, stroke, impotence (e.g., due to disease, and disease, stroke, impotence) (e.g., due to disease, stroke, impotence) (e.g., due to disease, engineer impotence) (e.g., due to disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease, engineer disease |
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| permethility, viscular tone, and minmure cell extravastion. Exemplary endothelial cells that may be used according to these assays include human unabilities usin endothelial cells (HUVEC), which sear awaither from commercial sources. The expression of VCAM, COTHOs, a member assays and protein, can be tupegaliated by optoxines or dother factors, and contributes to the extravastation of hymphocytes, lean-extravastion of hymphocytes, lean-extravastion of minmure cells from blood vessels, thus VCAM expression plays a node minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure and minmure an | Assays for measuring accretion of insulin are well-known in the art and may be used or notmetry modified to assess the ability of polygopides of the invention (including multhodies of the invention) to simulate managemiss of the invention to simulate insulin accretion. For example, insulin ascerction for example, insulin ascerction from panceatic between the ability of the properties of the international properties of the international production of the properties of the properties of the properties of the properties of the production of the properties of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the prod |
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| microvascular disease, hypertension,<br>sroke, and other diseases and<br>disorders as described in the<br>"Cardiovascular Disorders" section<br>below), dyslipidemia, endocrine         | disorders (as described in the "Findocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and bindness), ulcers and impaired wound healing, and infection (e.g., milectous diseases and disorders as | Diseases" section below, especially besched in the 'Intlections Diseases' section below, especially of the unimary treat and skin), carpal tunnel syndrome and Dupluyerer's An additional syndrome and Dupluyerer's An additional begin preferred indication is obesity. Additional highly preferred indication is obesity. Additional highly preferred indications include weight loss or harmaroly, weight gain. Additional highly preferred indications are complications are complications are soundications are complications.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | A highly preferred indicaton is diabetes mellins.  diabetes mellins.  additional highly preferred indication is a complication associated with fallence (e.g. diabetic reimposity, diabetic melliners (e.g. diabetic reimposity, diabetic melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, melliner, me |
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| antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt.2)R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9<br>(1995); and. Miragias S et. al.,<br>Lournal of Biomolecular Sercening,<br>4:193-204 (1999), the contents of<br>each of which is herein incorporated<br>by reference in its entirety.                    | evocating to these assays are publicly available (e.g., through the ATCCP). Exemplary punceatic cells that may be not may be routinely generated. Exemplary punceatic cells that may be not according to these assays include at INS-1 cells are are a semi-addressert cell line established from cells isolated from any A-ray induced for transplantable maintona. These cells reduit characteristics typical of matve glucose inducible insulin secretion. The deferrores, shaft et al. Effectives, nducible insulin secretion. | seasops for measuring existing that are well-known in the art and may be add or rountingly modified to assess the ability of polypeptides of the method of polypeptides of the article (including anthodies and agonists or antagonists of the article (including anthodies and agonists or antagonists of the complete the ELPR assay may be example: the ELPR assay may be feed to measure infinite of calcium. For the article of the article and the collision.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| - | nerve disease and nerve damage     | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental  | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart  | discase, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and        | disorders as described in the         | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision     | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as  | described in the "Infectious           | Discases" section below, especially     | of the urinary tract and skin), carpal | me a                                  | contracture). An additional                  | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain.       | Aditional highly preferred           | indications are complications       | associated with insulin resistance. |                                       |                                    |
|---|------------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|------------------------------|-----------------------------------|----------------------------------|--------------------------------------|---------------------------|--------------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|--------------------------------|-------------------------------|--------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------------|---------------------------------------|----------------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|------------------------------------|
|   | concentrations of cytosonic calcum | compared to much higher             | extracellular calcium. Extracellular  | factors can cause an influx of  | calcium, leading to activation of   | calcium responsive signaling | pathways and alterations in cell  | functions. Exemplary assays that | may be used or routinely modified to | measure calcium flux by   | polypeptides of the invention        | (including antibodics and agonists or | antagonists of the invention) include | assays disclosed in: Satin LS, et al., | Endocrinology, 136(10):4589-601 | (1995);Mogami H, et al.,       | Endocrinology, 136(7):2960-6  | (1995); Richardson SB, et al., | Biochem J, 288 ( Pt 3):847-51          | (1992); and, Meats, JE, et al., Cell | Calcium 1989 Nov-Dec;10(8):535-41   | (1989), the contents of each of which | is herein incorporated by reference in | its entirety. Pancreatic cells that may | be used according to these assays are  | publicly available (e.g., through the | ATCC <sup>TM</sup> ) and/or may be routinely | generated. Exemplary pancreatic        | cells that may be used according to  | these assays include HITT15 Cells.   | HITT15 are an adherent epithelial  | cell line established from Syrian | hamster islet cells transformed with | SV40. These cells express glucagon, | somatostatin, and glucocorticoid    | receptors. The cells secrete insulin, | which is stimulated by glucose and |
| - |                                    |                                     |                                       |                                 |                                     |                              |                                   |                                  |                                      |                           |                                      |                                       |                                       |                                        |                                 |                                |                               |                                |                                        |                                      |                                     |                                       |                                        |                                         |                                        |                                       |                                              |                                        |                                      |                                      |                                    |                                   |                                      |                                     |                                     |                                       |                                    |
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|     |         |     |                                                   | glucagon and suppressed by<br>somatostatin or glucoordicoids.<br>ATTC#CRL-1777 Refsi: Lord and<br>Asheroti. Biochem J. 219: 547-551;<br>Santerre et al. Proc. Natl. Acad. Sci.<br>USA 78: 4339-4443; 1981.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| 961 | нковров | 009 | Regulation of grophosis in pamorentic bota cells. | Segmes Apoptonis Assays for caspass apoptonis a raw well known in modified to assess the ability of properties of the area of more based or notation of apoptopics, or the invention of the properties of the invention of the properties of the invention of the properties of the invention of angeonists of the invention of apoptosis. Apoptosis in pattern of the propersion of the fact as associated with induction and propersion of dialectes. Exempling the associated with induction and propersion of dialectes. Exempling the season of clarkets, and the propersion of dialectes. Exempling the season of clarkets are applied as the arm of polypeptides of the invention of objective and the propersion of the fact. Properties and agonisis of the invention included antageomists of the invention included and assess of each age and in PRISE Lett. 460(3):283-84 (1906); Saint. K. et al., Jimmannol. 1294(4):687-94 (1900); Teiged. J. et al., FIRBS Lett. 450(2):238-36 (1909); Lett. 459(2):238-36 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909); Lett. 455(2):315-30 (1909) | A highly preferred indication is diahetes mellins.  A highly preferred indication is a complication associated with distinct of the preferred indication is a complication associated with dishers (e.g. indiahetic retinopality, disheric regionality, disheric regionality, and dishers (e.g. indiahetic regionality, disheric regionality, disheric regionality, disheric regionality, disheric regionality, increve diseases and diseases and diseases and diseases and disease and nerve damage. A centrol biological product neuropality, nerve disease and nerve damage. A centrol product neuropality, how diverse in the disease and nerve damage of the companity or blood vessel blookage, heart disease, mental contaison, downsiness, mortal contaison, downsiness, downsines |

| an, J. Figure 1. See J. | Assays for the regulation of A highly preferred indications is attrasterption through the DMFF!  A creates element are well-known in performed indications include the net and may be used or nontinely complications associated with modified to assess the ability of dishers (e.g., retal failure, nephropathy antagonists of the invention) to advise the DMFF! response defensed in a reporter constant (see, a retal failure, nephropathy antagonists of the invention) to advise the DMFF! response described in the Yearal Dissorbers' element in a reporter constant (see, because and nerve disasses and dissorbers as a state containing the GLUF4 in promoted of the proposal containing the GLUF4 in the contraining the GLUF4 disheric neuropathy, procupation. The DMFF response demand is production. The DMFF response blood vessel blookage, heart disease, element is present in the GLUF4 disheric neuropathy and the patient installing. |
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| blockage), seizures, mental      | confusion, drowsiness, nonketotic     | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,     | microvascular disease, hypertension,  | stroke, and other diseases and      | disorders as described in the | "Cardiovascular Disorders" section  | below), dyslipidemia, endocrine     | disorders (as described in the     | "Endocrine Disorders" section       | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious      | Diseases" section below, especially | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications    | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight | gain. Additional highly preferred | indications are complications  | associated with insulin resistance. |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |
| transcription factor and another | transcription factor that is required | for insulin regulation of Glut4  | expression in skeletal muscle.      | GLUT4 is the primary insulin- | responsive glucose transporter in fat | and muscle tissue. Exemplary assays | that may be used or routinely | modified to test for DMEF1 response | element activity (in adipocytes and | pre-adipocytes) by polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed    | inThai, M.V., et al., J Biol Chem,  | 273(23):14285-92 (1998); Mora, S.,  | et al., J Biol Chem, 275(21):16323-8 | (2000); Liu, M.L., et al., J Biol | Chem, 269(45):28514-21 (1994);      | "Identification of a 30-base pair  | regulatory element and novel DNA       | binding protein that regulates the | human GLUT4 promoter in             | transgenic mice", J Biol Chem. 2000  | Aug 4;275(31):23666-73; Berger, et   | al., Gene 66:1-10 (1988); and,    | Cullen, B., et al., Methods in | Enzymol. 216:362-368 (1992), the    | contents of each of which is herein | incorporated by reference in its | entirety. Adipocytes and pre- | adipocytes that may be used | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary cells that may be used | according to these assays include the |
|                                  |                                       |                                  |                                     |                               |                                       |                                     |                               |                                     |                                     |                                    |                                     |                                    |                                        |                                     |                                     |                                      |                                   |                                     |                                    |                                        |                                    |                                     |                                      |                                      |                                   |                                |                                     |                                     |                                  |                               |                             |                                        |                                      |                                    |                                  |                                       |
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| 197 | HSAWD74 | 109 | transcription through the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the constraint of the cons | activation of the NFAT signaling activation of the NFAT signaling activation of the NFAT signaling activation of NFAT in mast cell line. Activation of NFAT in mast cells has been linked to oytokine and chemical production. Assays for the activation of transcription for the activation of transcription of the activation of transcription of the activation of transcription in the art may be used or routinely of properties of the invention of the transcription for the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of the activation of including antibodies and agoniss or authorists and authorises and agoniss or authorised in intensication includes and agoniss or authorised in Bernzet et al., assays disclosed in Bernzet et al., assays disclosed in Bernzet et al.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Highly preferred inficiations include allergy seature, and riminist and distribute allergy seature, and riminist and distribute and distribute and distribute and distribute and distribute an include include (e.g., an infection include include and infinematory distributed infinematory distributed infinematory and infinematory was a proposite and information and infinematory and include an infinematory. *Tallord Referred infinematory and Discorders', Preferred infinemator discorders (e.g., as include and infinemator discorders (e.g., as infinematoricate) (e.g., as and/or as described below) and immunous discorders (e.g., as described below). Preferred infinematory includents in prediction in indications in infinematory includents in Preferred in infinematory in includents in particle reposition in finematory in includents in indications in includent in including includers in Preferred in infinitely intercents and or as described below under *Typerproprietrative*.) Other preferred |
|     | -       |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | and modilate version of geness<br>involved in immunomodilation of<br>modiscins. Escapplary assays for<br>transcription through the WFAT<br>response element that may be used or<br>municip modified to test WAT-<br>response element activity of<br>response element activity of<br>the invention of<br>the invention of<br>the invention of<br>antagonists of the invention) include<br>antagonists of the invention) include<br>antagonists of the invention) include<br>activity of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities of the invention include<br>activities |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| 601 Proliferation of pre- adipose cells (such as 3T3-L1 cells) | Malin, Methode in Enzymonel disproliticinus, and pre- Proc Nation Acad Sci USA 85:642— 364 (1988), De Boer et al., Int.) Biocher cel Bio 31 (1912) 1213 Biocher cel Bio 31 (1912) 1213 Intelnitions and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol Huddinson and McChosko, J Biol  | in conceases or decreases) of viability and proliferation of cells in vitro are proliferation of cells in vitro are proliferation of cells in vitro are seed or routinely modified to assess test of routinely modified to assess test of routinely modified to assess the ability of polypoptides of the aponists or antigonise of the agonists or antigonise of the agonists or antigonise of the proliferation of rive-adipose cells and proliferation of rive-adipose cells and cell lines. For example, the |
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|                                                                | Malin, Meliodas in Enzymon et al. 16:362-368 (1992); Itenthom et al. 16:362-368 (1992); Itenthom et al. 16:40-16:406 (1998); De Boer et al., Int. 16:40-6(1994); Ali et al., Immunol (1999); Ali et al., Immunol (1699); Ali et al., Impulso (1699); Ali et al., Impulso (1699); Ali et al., Impulso (1698); Ali et al |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSAWD74 601                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| Vinhility Assay (Promega Corp., Makalon, W. 1874) van he used to measure the number of vinhe cells in measure the number of vinhe cells in the best of undantiation of the ATP present which signals the events of metabolically active cells. 373-41, is a mouse continuous substant of 733 continuous substant of 733 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous substant of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 continuous of 734 contin | transacription through the Sermm<br>Response Element (SRE) are well-<br>kneyon in the art and may be used or<br>nothinely modified to assess the mainty of polyperides of the<br>invention (including autholicis and<br>major is of an agreement of the invention (including autholicis and<br>invention) to regulate the serum<br>response factors and modifiate the<br>cryptession of genes involved in<br>invention) to regulate the serum<br>response factors and modifiate the<br>expression of genes involved in<br>growth. Exemplary assays for<br>transcription through for Ele Diappendies<br>of the invention (including autholicis<br>of the invention (including autholicis<br>invention) include assays disclosed in<br>invention) include assays disclosed in<br>invention) include assays disclosed in<br>invention) Malin. Methods in |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Archaelon of transcription through scrum response element in immune cells (such as T-eelis).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 603                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSDEK49                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 198                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| mediated immune response, and<br>suppressing a T cell-mediated<br>immune response. Additional highly<br>mediated indications include      | preserved indications include inflammation and inflammatory disorders, and treating joint damage                | in patients with rheumatoid arthritis.  An additional highly preferred    | indication is sepsis. Highly<br>preferred indications include                       | neoplastic diseases (e.g., leukemia,<br>lymphoma, and/or as described | below under "Hyperproliferative  | Disorders"). Additionally, highly<br>preferred indications include | neoplasms and cancers, such as, for | example, leukemia, lymphoma, | melanoma, glioma (e.g., malignant | breast ling colon nancreatic | esophageal, stomach, brain, liver and | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | avannela hunamlasia matanlasia | and/or dysplasia. Preferred | indications include anemia, | pancytopenia, leukopenia, | thrombocytopenia, Hodgkin's | disease, acute lymphocytic anemia | (ALL), plasmacytomas, multiple | myeloma, Burkitt's lymphoma, | arthritis, AIDS, granulomatous | disease, inflammatory bowel disease, | neutropenia, neutrophilia, psoriasis, | Suppression of immine reactions to |
|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------|-------------------------------------|------------------------------|-----------------------------------|------------------------------|---------------------------------------|---------------------------------|----------------------------|-------------------------------------|--------------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------------|--------------------------------|------------------------------|--------------------------------|--------------------------------------|---------------------------------------|------------------------------------|
| Enzymol 216:362-368 (1992);<br>Henthorn et al., Proc Natl Acad Sci<br>USA 85:6342-6346 (1988); and<br>Black et al. Virus Games 12(2):105. | Diack et al., virus centes 12(2):103-<br>117 (1997), the content of each of<br>which are herein incorporated by | reference in its entirety. T cells that<br>may be used according to these | assays are publicly available (e.g.,<br>through the ATCC <sup>TM</sup> ). Exemplary | mouse T cells that may be used                                        | CTLL cell line, which is an IL-2 | dependent suspension culture of T cells with cytotoxic activity.   |                                     |                              |                                   |                              |                                       |                                 |                            |                                     |                                |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       |                                    |
|                                                                                                                                           |                                                                                                                 |                                                                           |                                                                                     |                                                                       |                                  |                                                                    |                                     |                              |                                   |                              |                                       |                                 |                            |                                     |                                |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       |                                    |
|                                                                                                                                           |                                                                                                                 |                                                                           |                                                                                     |                                                                       |                                  |                                                                    |                                     |                              |                                   |                              |                                       |                                 |                            |                                     |                                |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       | _                                  |
|                                                                                                                                           |                                                                                                                 |                                                                           |                                                                                     |                                                                       |                                  |                                                                    |                                     |                              |                                   |                              |                                       |                                 |                            |                                     |                                |                             |                             |                           |                             |                                   |                                |                              |                                |                                      |                                       | _                                  |

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| 861 | HSDEK49 | 602 | Regulation of Unite Enzyme in adiposytes | transcription of Malic Enzyme are worked-known in the art and tony be used erroutinely modified to assess the ability of polypeptides of the ability of polypeptides of the apility of polypeptides of the agents of the ability of polypeptides of the agents of rangonisis of the agents of rangonisis of the agents f the agent (IRP). He agent (IRP) He and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may also responds to API and other may be used or routinely margin of Malic Enzyme (if a propriet of Malic Enzyme (if a propriet of Malic Enzyme (if a propriet of Malic Enzyme (if a propriet of Malic Enzyme (if a propriet or magnosis of the invention) including supplying and API and other invention) includic assays diselected invention including and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API and API a | A highly preferred indication is diabetes mellins and additional highly preferred indication and additional highly preferred indication thinks and additional highly preferred indication thinks are complication associated with thinks and the preferred indication thinks are the season and indicate temporality, kiltray disease (e.g., trend infine, traphropathy method to the company, kiltray diseases and diseases and disease and disease and disease and disease and disease and disease to the companity. In the companity in the West in the West in the West in the West in the West in the West in the West in the West in the West in the Cell, the to diabetic neuropathy or blood vessel blockegs, heart disease, such and contributed the sease, and there of each of the west in the west in method to sease, a three proper season and diseased and these diseases as and diseased and these diseases as and diseased and these diseases as and diseased and these diseases as and diseased was described in the belowy despitiedmin, emboding to the internal methods to the described in the internal and the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property |
|     |         |     |                                          | Garcia-Jimenez, C., et al., Mol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | below), neuropathy, vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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|                                                                                                                                                                                                                               | Regulation of Assays for the regulation of Assays for the regulation of Assays for the regulation of Particle Assays for the regulation of Particle Assays for the regulation of the assays of the research of polygodides of the investigin of polygodides of the investigin of polygodides of the investigin of polygodides of the investigin of the particle and agonists or activate the PEPCK promozer in a reporter construction and regulated liver glabotomogenesis. Exemplary assays for regulation of the DEPCK promozer than though the PEPCK promozer than though the PEPCK promozer than though the PEPCK promozer activity of the set for PEPCK promozer than though the PEPCK promozer than though the PEPCK promozer than though the PEPCK promozer than the perfect promozer activity of the set for PEPCK promozer activity of the invention (including authorities of the invention) includes assays desided in present of the promozer activity of the invention includes assays desided in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                               | 603                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                               | HSDF/26                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|                                                                                                   |                                                                                                         | -                                                                          | below), neuropathy, vision  e in impairment (e.g., diabetic retinopathy at and blindness), ulcers and impaired |                                                                     | nay be described in the "Infectious<br>y liver Diseases" section below, especially  | -                               | _                                     | _                                   |                                   | opesity. Additional mgmy preferred indications include weight loss or | alternatively, weight gain. Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | musculoskeletal systems including | myopathies, muscular dystrophy, | and/or as described herein. | indications include glycogen storage | disease (e.g., glycogenoses), | hepatitis, gallstones, cirrhosis of the | liver, degenerative or necrotic liver |
|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------|---------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------|-------------------------------|-------------------------------------|-----------------------------|-----------------------------------|---------------------------------|-----------------------------|--------------------------------------|-------------------------------|-----------------------------------------|---------------------------------------|
| Berger et al., Gene 66:1-10 (1998);<br>Cullen and Malm, Methods in<br>Enzymol 216:362-368 (1992); | Henthorn et al., Proc Natl Acad Sci<br>USA 85:6342-6346 (1988);<br>Lochhead et al., Diabetes 49(6):896- | 903 (2000); and Yeagley et al., J Biol<br>Chem 275(23):17814-17820 (2000), | the contents of each of which is<br>herein incorporated by reference in<br>its entirety. Henatocyte cells that | may be used according to these assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ) and/or may be routinely generated. Exemplary liver | hepatoma cells that may be used | H4lle cells, which contain a tyrosine | amino transferase that is inducible | with glucocorticoids, insulin, or | CAIMP derivatives.                                                    |                                                         |                               |                                     |                             |                                   |                                 |                             |                                      |                               |                                         |                                       |
|                                                                                                   |                                                                                                         |                                                                            |                                                                                                                |                                                                     |                                                                                     |                                 |                                       |                                     |                                   |                                                                       |                                                         |                               |                                     |                             |                                   |                                 |                             |                                      |                               |                                         |                                       |

|     |         |     |                      |                                  | fibrosis, liver regeneration, metabolic |
|-----|---------|-----|----------------------|----------------------------------|-----------------------------------------|
|     |         |     |                      |                                  | disease, dyslipidemia and cholesterol   |
|     |         |     |                      |                                  | metabolism, and hepatocarcinomas.       |
|     |         |     |                      |                                  | Highly preferred indications include    |
|     |         |     |                      |                                  | blood disorders (e.g., as described     |
|     |         |     |                      |                                  | below under "Immune Activity",          |
|     |         |     |                      |                                  | "Cardiovascular Disorders", and/or      |
|     |         |     |                      |                                  | "Blood-Related Disorders"), immune      |
|     |         |     |                      |                                  | disorders (e.g., as described below     |
|     |         |     |                      |                                  | under "Immune Activity"), infection     |
|     |         |     |                      |                                  | (e.g., an infectious disease and/or     |
|     |         |     |                      |                                  | disorder as described below under       |
|     |         |     |                      |                                  | "Infectious Disease"), endocrine        |
|     |         |     |                      |                                  | disorders (e.g., as described below     |
|     |         |     |                      |                                  | under "Endocrine Disorders"), and       |
|     |         |     |                      |                                  | neural disorders (e.g., as described    |
|     |         |     |                      |                                  | below under "Neural Activity and        |
|     |         |     |                      |                                  | Neurological Diseases").                |
|     |         |     |                      |                                  | Additional preferred indications        |
|     |         |     |                      |                                  | include neoplastic diseases (e.g., as   |
|     |         |     |                      |                                  | described below under                   |
|     |         |     |                      |                                  | "Hyperproliferative Disorders").        |
|     |         |     |                      |                                  | Preferred indications include           |
|     |         |     |                      |                                  | neoplasms and cancers, such as,         |
|     |         |     |                      |                                  | leukemia, lymphoma, prostate,           |
|     |         |     |                      |                                  | breast, lung, colon, pancreatic,        |
|     |         |     |                      |                                  | esophageal, stomach, brain, and         |
|     |         |     |                      |                                  | urinary cancer. A highly preferred      |
|     |         |     |                      |                                  | indication is liver cancer. Other       |
|     |         |     |                      |                                  | preferred indications include benign    |
|     |         |     |                      |                                  | dysproliferative disorders and pre-     |
|     |         |     |                      |                                  | neoplastic conditions, such as, for     |
|     |         |     |                      |                                  | example, hyperplasia, metaplasia,       |
|     |         |     |                      |                                  | and/or dysplasia.                       |
|     | HSDJA15 | 604 | Activation of        | Kinase assay. Kinase assays, for | A highly preferred embodiment of        |
| 200 |         |     | Adipocyte PI3 Kinase | example an GSK-3 assays, for PI3 | the invention includes a method for     |
|     |         |     | Signalling Pathway   | kinase signal transduction that  | increasing adipocyte survival An        |

| alternative highly preferred<br>embodiment of the invention<br>includes a method for decreasing<br>adipocyte survival. A preferred<br>embodiment of the invention<br>includes a method for stimulating<br>adinovets melliferation. An                                                                                                      | alternative highly preferred alternative highly preferred includes amethod for inhibiting adipocyte proliferation. A adversarion proliferation. A investment proliferation. A investment proliferation in the investment proliferation. A advantage at method for any advantage at method for any advantage and advantage and a preferred propographic of the preferred propographic and preferred any advantage and advantage and a preferred propographic and any advantage and a preferred and a preferred propographic and any advantage and a preferred propographic and a preferred propographic and any advantage and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a preferred propographic and a propographic and a | and that the transfer of the investion of the investion of the investion of the investion of the investion of the investion of the investion of the investion of the investigation. Highly percent discisoins include endocrine discoders (e.g., as described below under "Endocrine of Stonders). Prefercent discissions include mophastic discusses (e.g., include neophastic discusses (e.g., include neophastic discusses (e.g., described below under a described below under                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | "Hyperpoliferative Disorders", hobod disorders (e.g., hypertension, congestive heart failure, blood disorders (e.g., hypertension, congestive heart failure, blood vessel importance and/or as described below importance and/or as described below. "Cardiovascular Disorders", and/or "Cardiovascular Disorders", and/or disorders (e.g., as described below under "Immune Activity", neural disorders (e.g., as described below under "Immune Activity"), neural under "Immune Activity", |
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| regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including amblodes and agoniss or antatomists of the invention) to antatomists of the invention to antatomists of the invention) to antatomists of the invention) to | amagement of an intensity to promote or mithing fattoose metabolism and cell survival.  Exemplary assays for FD Stimes activity that may be used or routinely modified to test PD Stimeso-induced activity of polypepides of the investigation (including antibodics and investigation (including antibodics and investigation (including antibodics and investigation (including autibodics and investigation).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | eguntas of antiquates to tare against a reading to the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the antiquate of the an | assays are publicly available (e.g., through the ATCCV). Exemplary mouse adhooyte cells that may be used according to these assays include 3T-L1 cells. 3T3-L1 is an albear mouse reachinoyte cell line that is a continus substrain of 3T3 fibrobias cells developed in through closal isolation and undergo a pre-adipocyce to adipoce-like conversion under appropriate conversion under appropriate conversion under appropriate differentiation conditions known in                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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                                                                                                 |

|  | th. | the art. | Neurological Diseases"), and           |
|--|-----|----------|----------------------------------------|
|  |     |          | infection (e.g., as described below    |
|  |     |          | under "Infectious Disease"). A         |
|  |     |          | highly preferred indication is         |
|  |     |          | diabetes mellitus. An                  |
|  |     |          | additional highly preferred indication |
|  |     |          | is a complication associated with      |
|  |     |          | diabetes (e.g., diabetic retinopathy,  |
|  |     |          | diabetic nephropathy, kidney disease   |
|  |     |          | (e.g., renal failure, nephropathy      |
|  |     |          | and/or other diseases and disorders as |
|  |     |          | described in the "Renal Disorders"     |
|  |     |          | section below), diabetic neuropathy,   |
|  |     |          | nerve disease and nerve damage (e.g.,  |
|  |     |          | due to diabetic neuropathy), blood     |
|  |     |          | vessel blockage, heart disease,        |
|  |     |          | stroke, impotence (e.g., due to        |
|  |     |          | diabetic neuropathy or blood vessel    |
|  |     |          | blockage), seizures, mental            |
|  |     |          | confusion, drowsiness, nonketotic      |
|  |     |          | hyperglycemic-hyperosmolar coma,       |
|  |     |          | cardiovascular disease (e.g., heart    |
|  |     |          | disease, atherosclerosis,              |
|  |     |          | microvascular disease, hypertension,   |
|  |     |          | stroke, and other diseases and         |
|  |     |          | disorders as described in the          |
|  |     |          | "Cardiovascular Disorders" section     |
|  |     |          | below), dyslipidemia, endocrine        |
|  |     |          | disorders (as described in the         |
|  |     |          | "Endocrine Disorders" section          |
|  |     |          | below), neuropathy, vision             |
|  |     |          | impairment (e.g., diabetic retinopathy |
|  |     |          | and blindness), ulcers and impaired    |
|  |     |          | wound healing, infection (e.g.,        |
|  |     |          | infectious diseases and disorders as   |
|  |     |          | described in the "Infectious           |
|  |     |          | Diseases" section below, especially    |

| of the urnary tract and skin), carpal turnel syndrome and Dypuytren's courteeture). An additional highly pretructed indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or allermatively world rain.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Additional highly preferred Additional highly preferred Additional highly preferred associated with insulin resistance Additional highly preferred indications are disorders of the musculoscheda systems including and/or as described herein.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a controller and a contro |
| kichtoy cencer. Additional highly preferred indications include melanoma, prostact, lang melanoma, prostact, lang beneratic, esophicagi, isomach, benin, liver, and uniany cancer. Over preferred indications include bening dyspoliterative disorders and pre-neoplastic conditions, such as, of example, hyperplassis, metaphasia, and of dysplassia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| A preferred embodiment of the | invention includes a method for | inhibiting (e.g., reducing) TNF alpha | production. An alternative preferred | embodiment of the invention      | ncludes a method for stimulating | (e.g., increasing) TNF alpha          | production. Preferred indications | include blood disorders (e.g., as | described below under "Immune | Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"), Highly preferred      | ndications include autoimmune             | liseases (e.g., rheumatoid arthritis,     | systemic lupus erythematosis, | Crohn"s disease, multiple sclerosis | and/or as described below), | immunodeficiencies (e.g., as             | described below), boosting a T cell- | nediated immune response, and | suppressing a T cell-mediated | mmune response. Additional highly | preferred indications include | nflammation and inflammatory | disorders, and treating joint damage | in patients with rheumatoid arthritis. | An additional highly preferred | ndication is sepsis. Highly | preferred indications include | reoplastic diseases (e.g., leukemia, | ymphoma, and/or as described               | below under "Hyperproliferative    | Disorders"). Additionally, highly     | preferred indications include  | neoplasms and cancers, such as, for<br>example, leukemia, lymphoma, |
|-------------------------------|---------------------------------|---------------------------------------|--------------------------------------|----------------------------------|----------------------------------|---------------------------------------|-----------------------------------|-----------------------------------|-------------------------------|---------------------------|------------------------------------|------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------|-------------------------------------|-----------------------------|------------------------------------------|--------------------------------------|-------------------------------|-------------------------------|-----------------------------------|-------------------------------|------------------------------|--------------------------------------|----------------------------------------|--------------------------------|-----------------------------|-------------------------------|--------------------------------------|--------------------------------------------|------------------------------------|---------------------------------------|--------------------------------|---------------------------------------------------------------------|
|                               |                                 |                                       | o pc                                 | routinely modified to assess the | ability of polypeptides of the   | invention (including antibodies and ( | agonists or antagonists of the    | invention) to regulate the serum  | 2                             |                           | _                                  | transcription through the SRE that | may be used or routinely modified to   ii | test SRE activity of the polypeptides   d | - 00                          | and agonists or antagonists of the  | d in                        | Berger et al., Gene 66:1-10 (1998);   ii |                                      | _                             | Sci                           |                                   | -                             | <u></u>                      | Ť                                    | that                                   | _                              |                             | ary I                         | mouse T cells that may be used n     | according to these assays include the   In | CTLL cell line, which is an IL-2 b | dependent suspension culture of T   I | cells with cytotoxic activity. | n<br>e                                                              |
| r                             | -                               | =                                     | cells (such                          | as T-cells).                     | B                                |                                       | B                                 | -8                                | 6                             | 9                         | OJ,                                |                                    | 4                                         | 3                                         | 0                             | 8                                   |                             |                                          |                                      |                               |                               |                                   |                               |                              | •                                    | 6                                      | -                              | 8                           | <u> </u>                      | u u                                  | B                                          |                                    | 9                                     | 3                              |                                                                     |
| 604                           |                                 |                                       |                                      |                                  |                                  |                                       |                                   |                                   |                               |                           |                                    |                                    |                                           |                                           |                               |                                     |                             |                                          |                                      |                               |                               |                                   |                               |                              |                                      |                                        |                                |                             |                               |                                      |                                            |                                    |                                       |                                |                                                                     |
| HSDJA15                       |                                 |                                       |                                      |                                  |                                  |                                       |                                   |                                   |                               |                           |                                    |                                    |                                           |                                           |                               |                                     |                             |                                          |                                      |                               |                               |                                   |                               |                              |                                      |                                        |                                |                             |                               |                                      |                                            |                                    |                                       |                                |                                                                     |
|                               | 200                             |                                       |                                      |                                  |                                  |                                       |                                   |                                   |                               |                           |                                    |                                    |                                           |                                           |                               |                                     |                             |                                          |                                      |                               |                               |                                   |                               |                              |                                      |                                        |                                |                             |                               |                                      |                                            |                                    |                                       |                                |                                                                     |

|         |     |                                                                                                   |                                                                                                                                                                                                             | menanoma, glionan (e.g., malignant glionan, soil tumors, and prostate, breast, lung, colon, pancrentic, espoipagal, somanda, brain, live and unitary cancer. Other preferred indications include benign dysponliterative disorders and pre-cample. It is a propositistic meditions, such as, for example. Appropriate, meditions, such as, for example. Appropriate, meditions, such as, for example, hyperplaisi, metaphasi, and dysponliterative disorders and pre-cample, hyperplaisi, metaphasi, partyoperia ledkoperia, furombocytoperia, luddgin's disease, and bymphocyte amenia disease, and bymphocyte amenia mychoma, and partyoperia, luddgin's disease, and promophila, poroviasis, suppression of immune reactions of sucher propriate and sease, inflammatory bowd disease, hermophila, hypercoagulation, hermophila, hypercoagulation, carriers, and sease, inflammatory bowd disease, hermophila, hypercoagulation, carriers, or homophila, hypercoagulation, carriers, or hermophila, hypercoagulation, carriers, or hermophila, hypercoagulation, carriers, or hermophila, procession sortius. |
|---------|-----|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |     |                                                                                                   |                                                                                                                                                                                                             | clasoctes mentals, accordants, meningits, Lyme Disease, cardiac reperfusion injury, and astlma and allergy. An additional preferred indication is infection (e.g., an infections) disease as described below minder infections. Disease as described below infections disease as described below.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HSDIA15 | 604 | Activation of transcription through GATA-3 response element in immune cells (such as mast cells). | This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to eyolóxice and chemokine production. Assays for | and innecessors present pro-<br>lighty preferred indications include<br>allergy, asthma, and rhinitis. Additional preferred indications<br>include infection (e.g., an infectious<br>disease as described below under<br>"Infectious Disease"), and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|         |     |                                                                                                   | the activation of transcription<br>through the GATA3 response                                                                                                                                               | inflammation and inflammatory<br>disorders. Preferred indications also                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                   | _                                                                 | _                                  | _                                     | _                                  | _                                    | _                                    | _                                   | _                                 | _                               | _                                    | _                                   | _                                 |                                | _                                     |                                       | _                                  | _                               | _                          | _                                    | _                                   | _                                 | _                           | _                             | _                             | _                                  | _                                   | _                                   | _                                    | _                                    | _                                   | _                                     | _                                      | _                                   | _                               | _                                    |
|-----------------------------------|-------------------------------------------------------------------|------------------------------------|---------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|
| include blood disorders (e.g., as | Activity" "Blood-Related                                          | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications    | include autoimmune diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple selerosis    | and/or as described below) and      | immunodeficiencies (e.g., as      | described below). Preferred     | indications include neoplastic       | discases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary    | tract cancers and/or as described     | below under "Hyperproliferative    | Disorders"). Other preferred    | indications include benign | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | thrombocytopenia, leukemias,       | Hodgkin's disease, acute            | lymphocytic anemia (ALL),           | plasmacytomas, multiple myeloma,     | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, sepsis, neutropenia,   | neutrophilia, psoriasis, suppression   | of immune reactions to transplanted | organs and tissues, hemophilia, | hypercoagulation, diabetes mellitus, |
| element are well-known in the art | and may be used or routinely<br>modified to assess the ability of | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to   | regulate GATA3 transcription factors | and modulate expression of mast cell | genes important for immune response | development. Exemplary assays for | transcription through the GATA3 | response element that may be used or | routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its    | entirety. Mast cells that may be used | according to these assays are publicly | available (e.g., through the        | ATCCTM). Exemplary human mast   | cells that may be used according to  |
|                                   |                                                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                 |                                      |
|                                   |                                                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                 |                                      |
|                                   |                                                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |                                        |                                     |                                 |                                      |

|     |        |     |                    | these assays include the HMC-1 cell<br>line, which is an immature human<br>mast cell line established from the<br>pertiheral blood of a patient with<br>mast cell lettkemia, and exhibits<br>many characteristics of immature<br>mast cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | endocarditis, meningitis, and Lyme<br>Disease.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----|--------|-----|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 300 | HSDA15 | 604 | Production of IL-5 | immunomodulatory proteins exercted immunomodulatory proteins exercted NTT Cells, master Cells, heasphilis, and cosinophilis that stimulate ecsinophili that stimulate ecsinophili that stimulate or CO3+ cells from TTZ cells are well more to marrian or CO3+ cells from TTZ cells are well more to marrian or CO3+ cells from TTZ cells are well more than the total control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or control or cont | A highly perfected embodiment<br>of the invention includes a method<br>for including LLS<br>production. An alternative lightly<br>preferred embodiment of the<br>simulating (e.g., increasing) LLS<br>production. An alternative lightly<br>preferred embodiment of the<br>simulating (e.g., increasing) LLS<br>production. An alternative lightly<br>production. An alternative lightly<br>preferred embodiment of the<br>moduleton and production. A<br>microal moduleton are settly of the<br>increasing immunoglobulin<br>preferred embodiment of the<br>increasing increasing in<br>immunoglobulin production. A<br>including (e.g., decreasing)<br>immunoglobulin production. A<br>altergy. A flightly preferred<br>altergy. A flightly preferred<br>altergy. A flightly preferred includes<br>altergy. A flightly preferred includes<br>altergy and include and alternative of the<br>highly preferred includional lightly<br>preferred includional lightly<br>preferred includional lightly<br>preferred includional lightly<br>perferred includional lightly<br>perferred includional lightly<br>preferred includional lightly<br>and ultiformatory on all immunosy-<br>and ultiformatory. |
|     |        |     |                    | mnnunonnoutlatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| A highly preferred embodiment    | of the invention includes a method                                          | proliferation. An alternative highly  | preferred embodiment of the          | invention includes a method for      | inhibiting adipocyte proliferation. | A highly preferred embodiment of    | the invention includes a method for | stimulating adipocyte differentiation. | An alternative highly preferred | embodiment of the invention           | includes a method for inhibiting     | adipocyte differentiation.        | highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | adipocyte activation. An alternative  | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | decreasing) and/or inactivating | adipocytes. Highly preferred        | indications include endocrine     | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           |
|----------------------------------|-----------------------------------------------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|---------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|------------------------------------|---------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| Kinase assay. Kinase assays, for | example an Elk-1 kinase assay, for<br>FRK eignal transduction that regulate | cell proliferation or differentiation | are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the  | invention (including antibodies and | agonists or antagonists of the      | invention) to promote or inhibit cell  | proliferation, activation, and  | differentiation. Exemplary assays for | ERK kinase activity that may be used | or routinely modified to test ERK | kinase-induced activity of         | polypeptides of the invention   | (including antibodics and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an |
| Activation of                    | Adipocyte ERK Signaling Pathygay                                            | fa                                    |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |
| 909                              |                                                                             |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |
| HSDJM31                          |                                                                             |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |
|                                  | 201                                                                         |                                       |                                      |                                      |                                     |                                     |                                     |                                        |                                 |                                       |                                      |                                   |                                    |                                 |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |

| "Cardiovascular Disorders", and/or "Blood-Related Disorders") immine       |                                | _                                    | disorders (e.g., as described below | Under "Neural Activity and<br>Naurological Disasses"), and |         | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | discase, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision |
|----------------------------------------------------------------------------|--------------------------------|--------------------------------------|-------------------------------------|------------------------------------------------------------|---------|------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|
| adherent mouse preadipocyte cell<br>line that is a continuous substrain of | 3T3 fibroblast cells developed | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | differentiation conditions brown in                        | the art |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |
|                                                                            |                                |                                      |                                     |                                                            |         |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |                            |
|                                                                            |                                |                                      |                                     |                                                            |         |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               | _                          |

|  | 1        | impairment (e.g., diabetic retinopathy  |
|--|----------|-----------------------------------------|
|  | -        | and blindness), ulcers and impaired     |
|  | <u> </u> | wound healing, infection (e.g.,         |
|  | i        | infectious diseases and disorders as    |
|  |          | described in the "Infectious            |
|  | 1        | Diseases" section below (particularly   |
|  |          | of the urinary tract and skin). An      |
|  |          | additional highly preferred indication  |
|  |          | is obesity and/or complications         |
|  | -        | associated with obesity. Additional     |
|  |          | highly preferred indications include    |
|  | _        | weight loss or alternatively, weight    |
|  |          | gain. Additional highly                 |
|  |          | preferred indications are               |
|  | 3        | complications associated with insulin   |
|  | 4        | resistance. Additional highly           |
|  |          | preferred indications are disorders of  |
|  |          | the musculoskeletal systems             |
|  | ·        | including myopathies, muscular          |
|  | -5       | dystrophy, and/or as described          |
|  |          | herein. Additional highly               |
|  |          | preferred indications include,          |
|  |          | hypertension, coronary artery           |
|  | 9        | disease, dyslipidemia, gallstones,      |
|  |          | osteoarthritis, degenerative arthritis, |
|  | -        | eating disorders, fibrosis, cachexia,   |
|  |          | and kidney diseases or disorders.       |
|  |          | Preferred indications include           |
|  |          | neoplasms and cancer, such as,          |
|  | _        | lymphoma, leukemia and breast,          |
|  | -        | colon, and kidney cancer. Additional    |
|  |          | preferred indications include           |
|  | н .      | melanoma, prostate, lung,               |
|  |          | pancreatic, esophageal, stomach,        |
|  |          | brain, liver, and urinary cancer.       |
|  | 1        | Highly preferred indications include    |
|  | _        | ipomas and liposarcomas. Other          |

| preferred indications include benign dysproliferative disorders and pre- neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. | s s t p p s s                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                  | Assays for the regulation of Iransaryiout hough the DMET response element are well-known in es the art and may be used or notutied) and after the mention of the invention) to activate the DMET response element in a reporter construct (such anatomists of the invention) to activate the DMET response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMET response element is present in the GLUT4 promoter and pinds to MET2 remessipion factor and another transarytion factor in the sequince for insulin regulation of Glauf expension in Stellar Inseparate CLUT4 is the primary insulin-regulation of Glauf another transarytion factor that is required for insulin regulation of Glauf presenting the productive of the section of the productive of the section of the invention (undired to test for DMET response and agonists or anagonists of the invention (including ambodies and agonists or anagonists of the invention (including ambodies and agonists or anagonists of the invention (including ambodies). |
|                                                                                                                                                                  | Regulation of transcription via DMEFI response clement in adipocytes and pre-adipocytes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                  | 909                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                  | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                  | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| Diseases' section telew especially client many care for the turnary treat and skin). An additional highly preferred indication as esterily and complications as esterily and complications include as esterily and complications include as esterily and containers by veight as well attensively, veight as many that never attensively, veight again. Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | A highly preferred indication is associated with observations associated with obesity. Additional highly preferred indications include weight loss of attentively, weight gan, and additional highly preferred modern in Safety weight gain. An additional highly preferred indication is disheven reallities. An additional highly preferred indication is disheven reallities. An additional highly preferred indication and indicators are difficulties.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Chem, 26(4)92,5814-21 (1994).  Redunfication of a 20 Hose pair regulatory element and moved DNA facilitations of element and moved DNA facilitations of element and moved DNA facilitations of L174 promoder in temperate in moved. J Blol Chem, 2000 Agray, 4275(3)12366-73; Breger, et al., Gene 66.1-10 (1988), and, Lenneymon, 126:362-386 (1992), the contents of eved of wheth is herein morporated by reference in its enemants of eved of wheth is herein moverporated by reference in its enemants of eved of wheth is the enemants of eved of wheth is the eventual of eved of which is the enemant of the eventual processing on these assays are publicly available (e.g., through the ATCCTP) and of may be unitiely generated. Exemplary cells that may be used Exemplary cells that may be used Exemplary cells that may be used eventing to these assays include the mouse 317-11 cells are a fallen from these and proposate and resolution. These cells undergo a pre- | Assays for the activation of Assays for the activation of Paracarpian that activation of Paracarpian that are and may be used or routinely modified to assays the ability of polyperbids of the invention opposes of the invention and activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation activation a |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Activation of<br>transcription through<br>cAMP response<br>element (CRE) in pre-<br>adipocytes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 909                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                                                                                                  | The state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|---------|-----|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HSI | HSDSB09 | 909 | Activation of reaction of reaction though remarchion though remarchion though in pre-adiposytes. | Assays for the activation of measurable the Semm-Response Element (SR3) are well-knear flowor in the art and may be used or outlinely modified to assays the based or outlinely modified to assays the invention (including antibodies of the invention (including antibodies and modified to assays the invention) to regulate the serum responses factors and modified the serum rescription through the SRE list in the acceptance of genes involved in growth. Exemplary assays for the acceptance of the properties of the invention (including antibodies SRE starvity of the polypsychiates of the invention) include assays disclosed in invention) include assays disclosed in invention include assays disclosed in invention include assays disclosed in invention include assays disclosed in invention include assays disclosed in vivention include and Main. Methods in invention include and Main. Methods in vivention in the control of each of the control of each of the other of the control of each of the control of each of the other or increme in its entirety. Proc dead of the control of each of the other or incention in tentirety. Proc outence is entirely.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | A highly preferred indication is sovering using associated with obesity. Additional absorption to substitute of the complications include weight loss or alternatively, weight weight loss or alternatively, weight indication is diabetes mellium. An additional highly preferred indication is additional highly preferred indication is a complication associated with insist occupients of the complication associated with its occupients of the complication associated with its actional highly referred indication is a complication associated with its occupients of the complication associated with its action in the Renal Disorders with the configuration of the complete in the Renal Disorders as and farer of disasses and darve damage (e.g., two to disheften neuropathy) blood vessel blockage, heart disease, can be only disheften neuropathy or blood vessel blockage, incurred ceg, due to disheften neuropathy or blood vessel blockage, incurred ceg, the or disheften neuropathy or blood vessel blockage, incurred ceg, the or disheften neuropathy or blood vessel blockage, incurred ceg, the or disheften neuropathy or blood vessel blockage, incurred ceg, the or disheften neuropathy or blood vessel blockage, incurred ceg. In part disease, althorocaterial disease, hypertension, arrowed, and other diseases and |

| Black et al., Virus Genes 12(2):105-        | preferred indications include          |
|---------------------------------------------|----------------------------------------|
| 117 (1997), the content of each of          | inflammation and inflammatory          |
| which are herein incorporated by            | disorders, and treating joint damage   |
| reference in its entirety. T cells that     | in patients with rheumatoid arthritis. |
| may be used according to these              | An additional highly preferred         |
| assays are publicly available (e.g.,        | indication is sepsis. Highly           |
| through the ATCC <sup>TM</sup> ). Exemplary | preferred indications include          |
| mouse T cells that may be used              | neoplastic diseases (e.g., leukemia,   |
| according to these assays include the       | lymphoma, and/or as described          |
| CTLL cell line, which is an IL-2            | below under "Hyperproliferative        |
| dependent suspension culture of T           | Disorders"). Additionally, highly      |
| cells with cytotoxic activity.              | preferred indications include          |
|                                             | neoplasms and cancers, such as, for    |
|                                             | example, leukemia, lymphoma,           |
|                                             | melanoma, glioma (e.g., malignant      |
|                                             | glioma), solid tumors, and prostate,   |
|                                             | breast, lung, colon, pancreatic,       |
|                                             | esophageal, stomach, brain, liver and  |
|                                             | urinary cancer. Other preferred        |
|                                             | indications include benign             |
|                                             | dysproliferative disorders and pre-    |
|                                             | neoplastic conditions, such as, for    |
|                                             | æ                                      |
|                                             | and/or dysplasia. Preferred            |
|                                             | indications include anemia,            |
|                                             | pancytopenia, leukopenia,              |
|                                             | thrombocytopenia, Hodgkin's            |
|                                             | disease, acute lymphocytic anemia      |
|                                             | (ALL), plasmacytomas, multiple         |
|                                             | myeloma, Burkitt's lymphoma,           |
|                                             | arthritis, AIDS, granulomatous         |
|                                             | disease, inflammatory bowel disease,   |
|                                             | neutropenia, neutrophilia, psoriasis,  |
|                                             | suppression of immune reactions to     |
|                                             | transplanted organs and tissues,       |
|                                             | hemophilia, hypercoagulation,          |
|                                             | diabetes mellitus, endocarditis,       |

| described in the "Infections seasons and disorders as described in the "Infections descenses" section below, especially of the urinary tree; and skin), carple unumel syndrome and Dapaytren; outment syndrome and Dapaytren; highly preferred indications to obesity and and the properties associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gam, alternatively, weight gam, alternatively, weight gam, alternatively, weight gam, alternatively, weight gam, alternatively, weight gam, alternatively, weight gam, alternatively preferred indications are complications associated with insulin resistance.                                                                                                               |                 | A highly preferred indication is diabetes mellinas. The A highly preferred indication is a complication state of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor of the angelor o |
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| 272(23)-2018/ed. Li Biol Chen,<br>727(23)-2018/ed. Li Biol Chen,<br>727(23)-2018/ed. Li Biol Chen,<br>727(23)-2018/ed. Li Biol Chen,<br>802(2)-2018/ed. Li Biol Chenosis<br>and, Cullera B. et al. Methods in<br>Benymol 216:522-368 (1992), the<br>Enzymol 216:522-368 (1992), the<br>Enzymol 216:522-368 (1992), the<br>Enzymol 216:222-368 (1992), the<br>mortures of each of which is herein<br>incomporated by reference in its<br>mortures. The propose of the<br>next according to these assoys are<br>used according to these assoys are<br>next according to these assoys are<br>that may be used according to these<br>that may be used according to these |                 | sasso for measuring election flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and any anguists or angeoins) or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins or angeoins of the angeoins or angeoins or or and the or or or or or or or or or or or or or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | SEAP in HIB/CRE | Stimulation of Calcium<br>Flux in pancreatic beta<br>cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 909             | 909                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HSDSB09         | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 202             | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                       | polypeptides of the invention           | microvascular disease, hypertension,   |
|-----|---------|-----|-----------------------|-----------------------------------------|----------------------------------------|
|     |         |     |                       | (including antibodies and agonists or   | stroke, and other diseases and         |
|     |         |     |                       | antagonists of the invention) include   | disorders as described in the          |
|     |         |     |                       | assays disclosed in: Satin LS, et al.,  | "Cardiovascular Disorders" section     |
|     |         |     |                       | Endocrinology, 136(10):4589-601         | below), dyslipidemia, endocrine        |
|     |         |     |                       | (1995);Mogami H, et al.,                | disorders (as described in the         |
|     |         |     |                       | Endocrinology, 136(7):2960-6            | "Endocrine Disorders" section          |
|     |         |     |                       | (1995); Richardson SB, et al.,          | below), neuropathy, vision             |
|     |         |     |                       | Biochem J, 288 ( Pt 3):847-51           | impairment (e.g., diabetic retinopathy |
|     |         |     |                       | (1992); and, Meats, JE, et al., Cell    | and blindness), ulcers and impaired    |
|     |         |     |                       | Calcium 1989 Nov-Dec;10(8):535-41       | wound healing, and infection (e.g.,    |
|     |         |     |                       | (1989), the contents of each of which   | infectious diseases and disorders as   |
|     |         |     |                       | is herein incorporated by reference in  | described in the "Infectious           |
|     |         |     |                       | its entirety. Pancreatic cells that may | Diseases" section below, especially    |
|     |         |     |                       | be used according to these assays are   | of the urinary tract and skin), carpal |
|     |         |     |                       | publicly available (e.g., through the   | tunnel syndrome and Dupuytren's        |
|     |         |     |                       | ATCCTM) and/or may be routinely         | contracture). An additional            |
|     |         |     |                       | generated. Exemplary pancreatic         | highly preferred indication is obesity |
|     |         |     |                       | cells that may be used according to     | and/or complications associated with   |
|     |         |     |                       | these assays include HITT15 Cells.      | obesity. Additional highly preferred   |
|     |         |     |                       | HITT15 are an adherent epithelial       | indications include weight loss or     |
|     |         |     |                       | cell line established from Syrian       | alternatively, weight gain.            |
|     |         |     |                       | hamster islet cells transformed with    | Aditional highly preferred             |
|     |         |     |                       | SV40. These cells express glucagon,     | indications are complications          |
|     |         |     |                       | somatostatin, and glucocorticoid        | associated with insulin resistance.    |
|     |         |     |                       | receptors. The cells secrete insulin,   |                                        |
|     |         |     |                       | which is stimulated by glucose and      |                                        |
|     |         |     |                       | glucagon and suppressed by              |                                        |
|     |         |     |                       | somatostatin or glucocorticoids.        |                                        |
|     |         |     |                       | ATTC# CRL-1777 Refs: Lord and           |                                        |
|     |         |     |                       | Ashcroft. Biochem. J. 219: 547-551;     |                                        |
|     |         |     |                       | Santerre et al. Proc. Natl. Acad. Sci.  |                                        |
|     |         |     |                       | USA 78: 4339-4343, 1981.                |                                        |
|     | HSDSB09 | 909 | Activation of         | This reporter assay measures            | Highly preferred indications include   |
| 202 |         |     | transcription through | activation of the GATA-3 signaling      | allergy, asthma, and rhinitis.         |
|     |         |     | GATA-3 response       | pathway in HMC-1 human mast cell        | Additional preferred indications       |
|     |         |     | element in immune     | line. Activation of GATA-3 in mast      | include infection (e.g., an infectious |

| disease as described below under      | "Infectious Disease"), and       | inflammation and inflammatory   | disorders. Preferred indications also | include blood disorders (e.g., as | described below under "Immune | Activity", "Blood-Related         | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications    | include autoimmune diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis    | and/or as described below) and      | immunodeficiencies (e.g., as      | described below). Preferred     | indications include neoplastic       | discases (e.g., leukemia, lymphoma, | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary    | tract cancers and/or as described     | below under "Hyperproliferative    | Disorders"). Other preferred    | indications include benign | dysproliferative disorders and pre-  | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | thrombocytopenia, leukemias,       | Hodgkin's disease, acute            | lymphocytic anemia (ALL),           | plasmacytomas, multiple myeloma,     | Burkitt's lymphoma, arthritis, AIDS, | granulomatous disease, inflammatory | bowel disease, sepsis, neutropenia,   |
|---------------------------------------|----------------------------------|---------------------------------|---------------------------------------|-----------------------------------|-------------------------------|-----------------------------------|------------------------------------|---------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|----------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|
| cells has been linked to cytokine and | chemokine production. Assays for | the activation of transcription | through the GATA3 response            | element are well-known in the art | and may be used or routinely  | modified to assess the ability of | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to   | regulate GATA3 transcription factors | and modulate expression of mast cell | genes important for immune response | development. Exemplary assays for | transcription through the GATA3 | response element that may be used or | routinely modified to test GATA3-   | response element activity of      | polypeptides of the invention  | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-     | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | of each of which are herein          | incorporated by reference in its    | entirety. Mast cells that may be used |
| cells (such as mast                   | cells).                          | •                               |                                       |                                   |                               |                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |
|                                       |                                  |                                 |                                       |                                   |                               |                                   |                                    |                                       |                                    |                                      |                                      |                                     |                                   |                                 |                                      |                                     |                                   |                                |                                       |                                       |                                    |                                 |                            |                                      |                                     |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                      |                                     |                                       |

|     |         |     |                                                                                               | to traces assays are puntory of the seasons are puntory of the seasons are puntory in the season are seasons are according to any be used according to a read according to a read and the seasons are as a season are as a season are as a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a season are a seas | of immune creations to transplanted of immune creations to transplanted transplanted are stories and instance herophiling, bypercoagulation, diabetes mellins, endocerditis, meningitis, and Lyme Discuss.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|---------|-----|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 202 | HSD5B09 | 909 | Activation of measurables through NFAT response cleared in immune cells (such as must cells). | This reporters assay measures acquired to when the acquired means of the acquired means of the acquired means of the acquired means of the acquired means of the acquired means of the acquired means of the activation of transcription. Assays for the activation of transcription acquired means acquired to exposite peans of the activation of transcription of the activation of transcription in the act and may be used or routinely acquired acquired and may be used or routinely ophypophics of the invention of including antibodies and agonisis or anticoding to assays the ability of polypophics of the invention in formation. Everyphary assays for transcription themselved in memorabulations. Everyphary assays for transcription themselved in memorabulations. Everyphary assays for transcription themselved in memorabulations. Everyphary acquired to test MFAT response element that may be used or response element activity of the invention.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Highty preferred indications included allery, safarin, and trinnis. Additional preferred indications. Additional preferred indications and the infections discusses as described below under fractions Discusses, and inflammation under inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation and inflammation discusses (e.g., networkers, preferred indications in the amounted infrarities, systemic lupus and arthritis, systemic lupus described below). Preferred discusses (e.g., lenternia, lymphoma, indications includine enoplastic discusses (e.g., lenternia, lymphoma, lance and lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, lymphoma, |
|     |         |     |                                                                                               | antagonists of the invention) include                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | below under "Hyperproliferative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|         |     |                       |                                        |                                         | - |
|---------|-----|-----------------------|----------------------------------------|-----------------------------------------|---|
|         |     |                       | assays disclosed in Berger et al.,     | Disorders"). Other preferred            |   |
|         |     |                       | Gene 66:1-10 (1998); Cullen and        | indications include benign              |   |
|         |     |                       | Malm, Methods in Enzymol               | dysproliferative disorders and pre-     |   |
|         |     |                       | 216:362-368 (1992); Henthorn et al.,   | neoplastic conditions, such as, for     |   |
|         |     |                       | Proc Natl Acad Sci USA 85:6342-        | example, hyperplasia, metaplasia,       |   |
|         |     |                       | 6346 (1988); De Boer et al., Int J     | and/or dysplasia. Preferred             |   |
|         |     |                       | Biochem Cell Biol 31(10):1221-1236     | indications include anemia,             |   |
|         |     |                       | (1999); Ali et al., J Immunol          | pancytopenia, leukopenia,               |   |
|         |     |                       | 165(12):7215-7223 (2000);              | thrombocytopenia, leukemias,            |   |
|         |     |                       | Hutchinson and McCloskey, J Biol       | Hodgkin's disease, acute                |   |
|         |     |                       | Chem 270(27):16333-16338 (1995),       | lymphocytic anemia (ALL),               |   |
|         |     |                       | and Turner et al., J Exp Med           | plasmacytomas, multiple myeloma,        |   |
|         |     |                       | 188:527-537 (1998), the contents of    | Burkitt's lymphoma, arthritis, AIDS,    |   |
|         |     |                       | each of which are herein               | granulomatous disease, inflammatory     |   |
|         |     |                       | incorporated by reference in its       | bowel disease, sepsis, neutropenia,     |   |
|         |     |                       | entirety. Mast cells that may be used  | neutrophilia, psoriasis, suppression    |   |
|         |     |                       | according to these assays are publicly | of immune reactions to transplanted     |   |
|         |     |                       | available (e.g., through the           | organs and tissues, hemophilia,         |   |
|         |     |                       | ATCCTM). Exemplary human mast          | hypercoagulation, diabetes mellitus,    |   |
|         |     |                       | cells that may be used according to    | endocarditis, meningitis, and Lyme      |   |
|         |     |                       | these assays include the HMC-1 cell    | Disease.                                |   |
|         |     |                       | line, which is an immature human       |                                         |   |
|         |     |                       | mast cell line established from the    |                                         |   |
|         |     |                       | peripheral blood of a patient with     |                                         |   |
|         |     |                       | mast cell leukemia, and exhibits       |                                         |   |
|         |     |                       | many characteristics of immature       |                                         |   |
|         |     |                       | mast cells.                            |                                         | _ |
| HSDSB09 | 909 | Activation of         | This reporter assay measures           | Highly preferred indication includes    |   |
|         |     | transcription through | activation of the NFkB signaling       | allergy, asthma, and rhinitis.          |   |
|         |     | NFKB response         | pathway in HMC-1 human mast cell       | Additional highly preferred             |   |
|         |     | element in immune     | line. Activation of NFkB in mast       | indications include infection (e.g., an |   |
|         |     | cells (such as mast   | cells has been linked to production of | infectious disease as described below   |   |
|         |     | cells).               | certain cytokines, such as IL-6 and    | under "Infectious Disease"), and        |   |
|         |     |                       | IL-9. Assays for the activation of     | inflammation and inflammatory           | _ |
|         |     |                       | transcription through the NFKB         | disorders. Preferred indications        | _ |
|         |     |                       | response element are well-known in     | include immunological and               |   |
|         |     |                       | the art and may be used or routinely   | hempatopoietic disorders (e.g., as      |   |

| г | _                                 | _                             | _                                     | _                                | _                                     | _                             | _                                    | _                                  | _                                 | _                                   | _                                   | _                                   |                                     |                                    |                                        |                                     |                                   |                                  |                                     |                                        |                                 |                                     |                                   |                                       |                                      |                                         |                                    |                                       |                                            |                                     | _                                   | _                                | _                                   |                                    |                                  | _                                | _           |
|---|-----------------------------------|-------------------------------|---------------------------------------|----------------------------------|---------------------------------------|-------------------------------|--------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------|----------------------------------|-------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|---------------------------------------|--------------------------------------|-----------------------------------------|------------------------------------|---------------------------------------|--------------------------------------------|-------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------|-------------|
|   | described below under "Immune     | Activity", and "Blood-Related | Disorders"). Preferred indications    | also include autoimmune diseases | (e.g., rheumatoid arthritis, systemic | lupus crythematosis, multiple | sclerosis and/or as described below) | and immunodeficiencies (e.g., as   | described below). Preferred       | indications also include neoplastic | diseases (e.g., leukemia, lymphoma, | melanoma, and/or as described below | under "Hyperproliferative           | Disorders"). Preferred indications | include neoplasms and cancer, such     | as, for example, leukemia,          | lymphoma, melanoma, and prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver,  | urinary tract cancers and as described | below under "Hyperproliferative | Disorders".                         |                                   |                                       |                                      |                                         |                                    |                                       |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             |
|   | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to | regulate NFKB transcription factors   | and modulate expression of    | immunomodulatory genes.              | Exemplary assays for transcription | through the NFKB response element | that may be used or rountinely      | modified to test NFKB-response      | clement activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in       | Enzymol 216:362-368 (1992);      | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Stassen       | et al, J Immunol 166(7):4391-8  | (2001); and Marquardt and Walker, J | Allergy Clin Immunol 105(3):500-5 | (2000), the contents of each of which | are herein incorporated by reference | in its entirety. Mast cells that may be | used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary human mast | cells that may be used according to | these assays include the HMC-1 cell | line, which is an immature human | mast cell line established from the | peripheral blood of a patient with | mast cell leukemia, and exhibits | many characteristics of immature | mast cells. |
|   |                                   |                               |                                       |                                  |                                       |                               |                                      |                                    |                                   |                                     |                                     |                                     |                                     |                                    |                                        |                                     |                                   |                                  |                                     |                                        |                                 |                                     |                                   |                                       |                                      |                                         |                                    |                                       |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             |
|   |                                   |                               |                                       |                                  |                                       |                               |                                      |                                    |                                   |                                     |                                     |                                     |                                     |                                    |                                        |                                     |                                   |                                  |                                     |                                        |                                 |                                     |                                   |                                       |                                      |                                         |                                    |                                       |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             |
|   |                                   |                               |                                       |                                  |                                       |                               |                                      |                                    |                                   |                                     |                                     |                                     |                                     |                                    |                                        |                                     |                                   |                                  |                                     |                                        |                                 |                                     |                                   |                                       |                                      |                                         |                                    |                                       |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             |
|   |                                   |                               |                                       |                                  |                                       |                               |                                      |                                    |                                   |                                     |                                     |                                     |                                     |                                    |                                        |                                     |                                   |                                  |                                     |                                        |                                 |                                     |                                   |                                       |                                      |                                         |                                    |                                       |                                            |                                     |                                     |                                  |                                     |                                    |                                  |                                  |             |

| nclude                               |                                  |                               | e.g., an                                | i below                              | pu                                  | 2.                               | ns also                               |                                    | , as                                | me                             |                              | cular                              | ases                              | temic                                |                                    | elow),                                | as                               |                                      |                                        | homa,                               | d below                                |                                     | ions                               | , such                            |                                     | ostate,                           |                                 | iver and                             | q                                    |                               | -ard                                | for,                                | ısia,                                |                                  | etic                                  | such as                                |
|--------------------------------------|----------------------------------|-------------------------------|-----------------------------------------|--------------------------------------|-------------------------------------|----------------------------------|---------------------------------------|------------------------------------|-------------------------------------|--------------------------------|------------------------------|------------------------------------|-----------------------------------|--------------------------------------|------------------------------------|---------------------------------------|----------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|------------------------------------|-----------------------------------|-------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|----------------------------------------|
| indications                          | nd rhinitis.                     | preferred .                   | le infection                            | as describe                          | Disease"), a                        | l inflammatc                     | red indicatio                         | pietic and                         | isorders (e.g                       | under "Immi                    | i-Related                    | r "Cardiova                        | immune dix                        | arthritis, sys                       | sis, multiple                      | s described                           | iencies (e.g.                    | . Preferred                          | le neoplastic                          | kemia, lym                          | r as describe                          | liferative                          | erred indicat                      | s and cancer                      | eukemia,                            | ioma, and pi                      | n, pancreatic                   | ach, brain, l                        | ther preferre                        | le benign                     | lisorders and                       | ions, such as                       | asia, metapl                         | Preferred                        | le hematopo                           | al disorders                           |
| Highly preferred indications include | allergy, asthma, and rhinitis.   | Additional highly preferred   | indications include infection (e.g., an | nfectious disease as described below | under "Infectious Disease"), and    | nflammation and inflammatory     | disorders. Preferred indications also | nelude hematopoietic and           | mmunological disorders (e.g., as    | described below under "Immune  | Activity", "Blood-Related    | Disorders", and/or "Cardiovascular | Disorders"), autoimmune diseases  | e.g., rheumatoid arthritis, systemic | upus erythematosis, multiple       | sclerosis and/or as described below), | and immunodeficiencies (e.g., as | described below). Preferred          | ndications include neoplastic          | liseases (e.g., leukemia, lymphoma, | nelanoma, and/or as described below    | inder "Hyperproliferative           | Disorders"). Preferred indications | nclude neoplasms and cancer, such | is, for example, leukemia,          | ymphoma, melanoma, and prostate,  | reast, lung, colon, pancreatic, | sophageal, stomach, brain, liver and | arinary cancer. Other preferred      | ndications include benign     | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia,    | and/or dysplasia. Preferred      | indications include hematopoietic     | and immunological disorders such as    |
| High                                 | alle                             | γq                            | _                                       |                                      | _                                   | in                               | Ť                                     | inc                                |                                     | ge                             | Ac                           | _                                  | Dis                               | Ť                                    | _                                  | scl                                   | and                              | -                                    |                                        | Ť                                   | _                                      | _                                   | Dis                                |                                   | 70                                  | _                                 | pre                             | _                                    | _                                    | ind                           | dy                                  | _                                   | -                                    | апс                              | _                                     |                                        |
| Jo t                                 | e Signal                         | tors of                       | response                                | s (such as                           | cell line)                          | id may be                        | icd to asse                           | es of the                          | ibodies an                          | of the                         | LAT6                         | l modulate                         | de genes.                         | anscription                          | sonse elerr                        | incly                                 | response                         | olypeptide                           | ing antiboo                            | ists of the                         | s disclose                             | -10 (1998)                          | ods in                             | 1992);                            | rtl Acad So                         | 88); Shern                        | 5 (2001);                       | Immunol                              | asuda et al                          | 31-29337                      | d., J Biol                          | (2001), d                           | th are here                          | c in its                         | may be u                              | s are publ                             |
| activation                           | hrough th                        | nd Activa                     | (STAT6)                                 | mune cells                           | AC-1 mast                           | the art ar                       | cly modifi                            | olypeptid                          | luding ant                          | tagonists o                    | regulate S'                  | actors and                         | ı of multip                       | says for tr                          | FAT6 resp                          | sed or rout                           | st STAT6                         | ty of the p                          | on (includi                            | r antagon                           | lude assay                             | Jene 66:1                           | alm, Meth                          | 362-368                           | I., Proc Na                         | -6346 (19                         | 179:48-50                       | Uckun, J                             | 2002); M                             | 5(38):293                     | fasuda et a                         | 107-26113                           | ch of whic                           | y reference                      | t cells that                          | hese assay                             |
| Assays for the activation of         | transcription through the Signal | Fransducers and Activators of | Transcription (STAT6) response          | element in immune cells (such as in  | the human HMC-1 mast cell line) are | well-known in the art and may be | used or routinely modified to assess  | the ability of polypeptides of the | invention (including antibodies and | agonists or antagonists of the | invention) to regulate STAT6 | transcription factors and modulate | the expression of multiple genes. | Exemplary assays for transcription   | through the STAT6 response element | that may be used or routinely         | modified to test STAT6 response  | element activity of the polypeptides | of the invention (including antibodies | and agonists or antagonists of the  | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in        | Enzymol 216:362-368 (1992);       | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Sherman, | Immunol Rev 179:48-56 (2001);   | Malaviya and Uckun, J Immunol        | 168:421-426 (2002); Masuda et al., J | Biol Chem 275(38):29331-29337 | 2000); and Masuda et al., J Biol    | Chem 276:26107-26113 (2001), the    | contents of each of which are herein | incorporated by reference in its | entirety. Mast cells that may be used | according to these assays are publicly |
| Ass                                  | tran                             | Tra                           | Tra                                     | cler                                 | the                                 | wel                              | nsc                                   | the                                | inve                                | ago                            | inv                          | tran                               | the                               | Exe                                  | thro                               | that                                  | moc                              | cler                                 | oft                                    | and                                 | inve                                   | Ber                                 | S                                  | Enz                               | Her                                 | ΩŠ                                | Imu                             | Maj                                  | 168                                  | Bio                           | (50                                 | g                                   | con                                  | inc                              | enti                                  | acc                                    |
| J.                                   | through                          | onsc                          | mmnne                                   | s mast                               |                                     |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |
| Activation of                        | transcription through            | STAT6 response                | element in immune                       | cells (such as mast                  | cells).                             |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |
| V                                    | =                                | S                             | 9                                       | 9                                    | 9                                   |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |
| 909                                  |                                  |                               |                                         |                                      |                                     |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |
| )9                                   |                                  |                               |                                         |                                      |                                     |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       | _                                      |
| HSDSB09                              |                                  |                               |                                         |                                      |                                     |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |
| HSI                                  |                                  |                               |                                         |                                      |                                     |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |
|                                      | 202                              |                               |                                         |                                      |                                     |                                  |                                       |                                    |                                     |                                |                              |                                    |                                   |                                      |                                    |                                       |                                  |                                      |                                        |                                     |                                        |                                     |                                    |                                   |                                     |                                   |                                 |                                      |                                      |                               |                                     |                                     |                                      |                                  |                                       |                                        |

|          |     |                                                                             | ATC(2**) Exemploy furnam must<br>ATC(2**) Exemploy furnam must<br>feel full may be used according to<br>these assays include the HMC-1 cell<br>line, which is an immature human<br>was cell line established from the<br>pertipleral blood of a patient with<br>must cell leukemia, and exhibits<br>must cell leukemia, and exhibits<br>must cell leukemia, and exhibits<br>must cell leukemia, and exhibits<br>must characteristics of immature<br>must cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ettimin, ALD, gramtonatoria, et servicio, et |
|----------|-----|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HSDSB099 | 909 | Scientifico of insulin<br>Scientifico de la collis-<br>parcenir beta cells. | insulin are well-known in the art and meaning accretion of assess the ability of polycyptides of the work of the polycyptides of the work of the polycyptides of the work of the polycyptides of the agentis or antagoniss of the invention (notability antibodes and agonis or antagoniss of the invention) to stimulate insulin secretion. For example, insulin secretion from panceauches and agonis on the polycyptides and the polycyptides of the in type and the polycyptides, and the polycyptides of the polycyptides of the from panceauch of the polycyptides of the from panceauch of insulin secretion (from panceauch cells) by ophypoptides of the five polycyptides and agonis or direction (including ambodies and agonis or direction (including ambodies and agonis or direction (polycyptides) and Alley 18, ct al., Endocrambogy, Li. M., et al., Endocrambogy, et al., ETBS LLI, 377(2):273-9. | h highly preferred indication is diabetes mellitus.  A highly preferred indication is a completion and season and season in a completion associated with instances (e.g., diabetic retinopality, kidney disease (e.g., tenal falture, nephropality, diabetic nephropality, kidney disease (e.g., tenal falture, nephropality, nerve diseases and diseators as described in the 'Renal Disouters' season below, ladente neuropality, nerve disease and nerve damage (e.g., the to diabetic neuropality). Blood vessel blockage, heart disease, carbo below, ladente neuropality or blood vessel blockage, nearly experience and contission, drowsiness, mental contission, drowsiness, mental contission, drowsiness, mental contission, drowsiness, mental contission, drowsiness, mental contission, drowsiness, mental contission, drowsiness, mental control singer (e.g., heart disease, singer desease, hyperedised seases, hyperedised seases, hyperedised singer diseases, and diseades as diseases, hyperedisease, and diseades as diseases, hyperedisease, and diseades as diseases, hyperedisease, and diseades as diseases, hyperediseases, and diseades as diseases, hyperediseases, and diseades as described in the 'Cardiovascular Tisonders' section disorders (e.g. described in the disorders) described in the disorders (e.g., heart disease, and described in the disorders) described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders as described in the disorders's described in the disorders's described in the disorders's described in the disorders's described in the disorders and described in the disorders and described in the disorders and described in the disorders and described in the disorders's described in the disorders and described in the disorders and described |

| modified to test NFKB-response dement activity of polyperjacks of the invention (including authorities and againsts or an against sor for the including authorities as for sealing size or an against sor for a for sealing size or an against sor for a for sealing size or an against sor for a for sealing size or an against sor an against sor for a for sealing size or an against sor for a for sealing size or an against sor for sealing sor for sealing size or an against sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for sealing sor for s | Assays for the activation of remarkable of the activation of the remacration through the Serum Response Element (SRE) are well-inhibiting (e.g., rechoicing TNF alpha known in the art and may be used or production. An attenuative lightly contined to assess the production. An attenuative lightly contined to assess the preferred embodiment of the hality of polypoptices of the invention indicates a method for invention in the production. The contined are all the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the production of the   |
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| modified I constituted the invent of characters and agents in eventually Berger et al. Cullera and Europana I Hardhom.  1524, 855 et al, Int. A. Ct. (14):20 et al. (11):40;20 | Activation Assays K<br>transcription through rurascription through rurascription through rurascription through in infrantuc cells (sach known in infrantuc cells (sach known in infrantuc cells (sach known in infrantuc cells (sach known in invention invention invention cells (sach known in interpretation |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Disorders," and/or "Cardiovascular molocules," and/or "Cardiovascular indications include autoimmune discussos (e.g., theramoid affritis, systemic lipus crythematoid affritis, systemic lipus crythematoids, systemic lipus crythematoids, and/or si dessent multiple selenxis and/or as described below), infimumone/fricarcias (e.g., as described below), to sosting a Teell-mediated immune response, and mediated immune response, and | immune response. Additional highly appressing Pt rectificational highly preferred indications include inflammation and inflammaton and the preferred in patients with rheumatoid arthritis. An additional highly preferred indication is negative, Highly preferred indications include preferred indications include the propositic disease (g., pletkerini, humbown, and/ore st-described inflammaton and/ore st-described inflammaton and/ore st-described inflammaton. | hydrona, who are accelerated below under "Hyperpoiliterative below under "Hyperpoiliterative below under "Hyperpoiliterative below under "Hyperpoiliterative below under "Hyperpoiliterative below "Hyperpoiliterative below "Hyperpoiliterative dexample, leukernit, lymphom, and methorona, glionor (e.g. miligmant glionn), soild unnors, and prostate, lung, color, pameratic, esophageal, stomach, brain, liver and glionny, and proposition calculous motude bening observed predictions, such as, for example, hyperplasia, metaplasia, despread of sysperplasia, metaplasia, cannule, hyperplasia, metaplasia, cannule, hyperplasia, metaplasia, metaplasia, metaplasia, metaplasia, metaplasia, preferred indications include anemia. Preferred indications include anemia. |
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| growth and upregulate the function of growth-relate genes in many cell types. Exempliary assays for transcription through the SRE that many the used or nothinely modified to SRE starting of the polypeptides of the invention (including authorities and agonists or armigonisis of the invention) including authorities and agonists or armigonisis of the struction) including seasyst declosed in being et al., Gene 66.1-10 (1999).    | Emzyma J 16:362-386 (1992),<br>Herdmorn et J., Froo Natl Acad Sci<br>Herdmorn et J., Froo Natl Acad Sci<br>USA 85:642-6346 (1988), Benson<br>et J., Immano I 15(9):380-2873<br>(1994); and Black et al., Virus Genes<br>12(2):105-117 (1997), the content of<br>each of which are beterin<br>incorporated by reference in its<br>morporated by reference in its<br>energy. T cells that may be used                                                                                                                                                                                        | writishle (e.g., through the ATCV-). Exercises a solid and a variable (e.g., through the may be used according to these may be used according to these works include the Nk-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| pancytopenia, letikopenia, fetikopenia, fetikora, fetikora, fetikora, fetikopenia, fetikora, fetikopenia, fet | allergy.  Another inighty prefered indication is altergy.  Another inighty  Another inighty  Additional lighty preferred  Additional lighty preferred indications is subma-  and inflammatory disorders.  Preferred indications include blood inflammatory disorders, and or Preferred indications include blood under "Immure Antivity", "Blood- Preferred indications include blood under "Immure Antivity", "Blood-  "Cardioviscaliar Disorders", and or "Cardioviscaliar Disorders", and or "Cardioviscaliar Disorders", "Bretter dindications is include autoimmure diseases (e.g., and or "Cardioviscaliar Disorders").  "Cardioviscaliar Disorders", and or "Cardioviscaliar Disorders", and or "Cardioviscaliar Disorders", and or "Cardioviscaliar Disorders", and or "Cardioviscaliar Disorders", and or se described below) and immunodeficiencies (e.g., as immunodeficiencies (e.g., as bettered indications include presented below) and immunodeficiencies (e.g., as bettered indications include Preferred Indicatio                                                                                                                                                             |
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|     |         |     |                   | antagonists of the invention) include<br>assays disclosed in Berger et al.,<br>Gene 66:1-10 (1998): Cullen and | neoplastic diseases (e.g., leukemia,<br>lymphoma, melanoma, and/or as<br>described helow under |
|-----|---------|-----|-------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|     |         |     |                   | Malm, Methods in Enzymol                                                                                       | "Hyperproliferative Disorders").                                                               |
|     |         |     |                   | 216:362-368 (1992); Henthorn et al.,<br>Proc Natl Acad Sci USA 85:6342-                                        | Preferred indications include<br>neoplasms and cancers, such as                                |
|     |         |     |                   | 6346 (1988); Georas et al., Blood                                                                              | leukemia, lymphoma, melanoma, and                                                              |
|     |         |     |                   | 92(12):4529-4538 (1998); Moffatt et                                                                            | prostate, breast, lung, colon,                                                                 |
|     |         |     |                   | al., Transplantation 69(7):1521-1523<br>(2000): Curiel et al., Eur J Imminol                                   | pancreatic, esophageal, stomach,<br>brain, liver and urinary cancer. Other                     |
|     |         |     |                   | 27(8):1982-1987 (1997); and Masuda                                                                             | preferred indications include benign                                                           |
|     |         |     |                   | et al., J Biol Chem 275(38):29331-                                                                             | dysproliferative disorders and pre-                                                            |
|     |         |     |                   | 29337 (2000), the contents of each of                                                                          | neoplastic conditions, such as, for                                                            |
|     |         |     |                   | which are herein incorporated by                                                                               | example, hyperplasia, metaplasia,                                                              |
|     |         |     |                   | reference in its entirety. T cells that                                                                        | and/or dysplasia.                                                                              |
|     |         |     |                   | may be used according to these                                                                                 | Preferred indications include anemia,                                                          |
|     |         |     |                   | assays are publicly available (e.g.,                                                                           | pancytopenia, leukopenia,                                                                      |
|     |         |     |                   | through the ATCCTM). Exemplary T                                                                               | thrombocytopenia, Hodgkin's                                                                    |
|     |         |     |                   | cells that may be used according to                                                                            | disease, acute lymphocytic anemia                                                              |
|     |         |     |                   | these assays include the SUPT cell                                                                             | (ALL), plasmacytomas, multiple                                                                 |
|     |         |     |                   | line, which is a suspension culture of                                                                         | myeloma, Burkitt's lymphoma,                                                                   |
|     |         |     |                   | IL-2 and IL-4 responsive T cells.                                                                              | arthritis, AIDS, granulomatous                                                                 |
|     |         |     |                   |                                                                                                                | disease, inflammatory bowel disease,                                                           |
|     |         |     |                   |                                                                                                                | sepsis, neutropenia, neutrophilia,                                                             |
|     |         |     |                   |                                                                                                                | psoriasis, suppression of immune                                                               |
|     |         |     |                   |                                                                                                                | reactions to transplanted organs and                                                           |
|     |         |     |                   |                                                                                                                | tissues, hemophilia,                                                                           |
|     |         |     |                   |                                                                                                                | hypercoagulation, diabetes mellitus,                                                           |
|     |         |     |                   |                                                                                                                | litis, menin                                                                                   |
|     |         |     |                   |                                                                                                                | Disease. An additional                                                                         |
|     |         |     |                   |                                                                                                                | preferred indication is infection (e.g.,                                                       |
|     |         |     |                   |                                                                                                                | an infectious disease as described                                                             |
|     |         |     |                   |                                                                                                                | below under "Infectious Disease").                                                             |
|     | HSHAX21 | 209 | Activation of     | Kinase assay. Kinase assays, for                                                                               | A highly preferred embodiment                                                                  |
| 203 |         |     | Adipocyte ERK     | example an Elk-1 kinase assay, for                                                                             | of the invention includes a method                                                             |
|     |         |     | Signaling Pathway | ERK signal transduction that regulate                                                                          | for stimulating adipocyte                                                                      |
|     |         |     |                   | cell proliferation or differentiation                                                                          | proliferation. An alternative highly                                                           |

| are well known in the art and may be preferred embodiment of the last of combinely under the ability of polypeptides of the mention in function (including amploties and agonists or antagonists of the mention) to promote or infahrical many being a mention includes a method for infahring art polyileration, activation, and differentiation. Activation, and differentiation. Activation, and differentiation. Activation, and differentiation. Activation in the invention includes a method for infahring or rotationally modified to test FIRK istanse-activity that may be used to the invention includes a method for infahring art polyileration, activation, and agonises of the invention) bridged in the invention includes a method for infahring and agonises of the invention) bridged in the invention includes a method for infahring the southern of the association of the invention of including arthories and agonises of the invention) bridged in the invention of the invention of including arthories and agonises of the invention) bridged in the invention includes a method for inhibiting and agonises of the invention includes a method for inhibiting and agonises of the invention includes a method for inhibiting and activation of the invention of the |
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| are well known in the art and may be used or notable; modified to assess the ability of polypeptides of the invention (including authories and aganists or antaganists of the invention) to horiding authories and aganists or antaganists of the invention including authories and aganists or antaganists of the invention of provided to use ERK kinase-adultity that may be tased or orating-unified to tase ERK kinase-adultity that may be tased or orating-unified to tase ERK kinase-adultity that may be tased or orating-unified to tase ERK kinase-adultity that may be tased or orating-unified to tase ERK kinase-adultity that may be tased to the invention) include the sawsy disolated in Ferra of all the invention) include the sawsy disolated in Ferra orating-unified to tase ERK kinase-adultity and the control of (1998). I. La Mandard-Bansel T. E.S. 1001 (1998). I. La Mandard-Bansel T. E.S. 1001 (1998). I. La Mandard-Bansel T. E.S. 1001 (1998). I. La Mandard-Bansel C. (2001), and Cobb. Mill Foreigness on the Article (1998). In Contraction of the against the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of the Article (1998). In Contraction of th |
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| differentiation conditions known in the art. |
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|                                              |
|                                              |

|  |      | described in the "Infections            |
|--|------|-----------------------------------------|
|  |      | reservoer in the internous              |
|  | _    | Diseases" section below (particularly   |
|  |      | of the urinary tract and skin). An      |
|  | -    | additional highly preferred indication  |
|  |      | is obesity and/or complications         |
|  |      | associated with obesity. Additional     |
|  | 4    | highly preferred indications include    |
|  |      | weight loss or alternatively, weight    |
|  | 0.00 | gain. Additional highly                 |
|  |      | ed i                                    |
|  | 3    | complications associated with insulin   |
|  | н    | resistance. Additional highly           |
|  |      | preferred indications are disorders of  |
|  | 1    | the musculoskeletal systems             |
|  |      | including myopathies, muscular          |
|  | -    | dystrophy, and/or as described          |
|  | 4    | nerein. Additional highly               |
|  |      | preferred indications include,          |
|  | -    | hypertension, coronary artery           |
|  |      | disease, dyslipidemia, gallstones,      |
|  |      | osteoarthritis, degenerative arthritis, |
|  |      | eating disorders, fibrosis, cachexia,   |
|  | 8    | and kidney diseases or disorders.       |
|  | 1    | Preferred indications include           |
|  | 1    | neoplasms and cancer, such as,          |
|  | 1    | lymphoma, leukemia and breast,          |
|  | -    | colon, and kidney cancer. Additional    |
|  | 1    | preferred indications include           |
|  | II . | melanoma, prostate, lung,               |
|  | 1    | pancreatic, esophageal, stomach,        |
|  |      | brain, liver, and urinary cancer.       |
|  | I    | Highly preferred indications include    |
|  | _    | lipomas and liposarcomas. Other         |
|  | -    | preferred indications include benign    |
|  | 9    | dysproliferative disorders and pre-     |
|  | 1    | neoplastic conditions, such as, for     |
|  | 0    | example, hyperplasia, metaplasia,       |

|     |         |     |               |                                         | and/or dysplasia.                       |
|-----|---------|-----|---------------|-----------------------------------------|-----------------------------------------|
|     | HSHAX21 | 209 | Production of | MIP-1alpha FMAT. Assays for             | A highly preferred embodiment           |
| 203 |         |     | MIPlalpha     | immunomodulatory proteins               | of the invention includes a method      |
|     |         |     |               | produced by activated dendritic cells   | for stimulating MIP1a production.       |
|     |         |     |               | that upregulate                         | An alternative highly preferred         |
|     |         |     |               | monocyte/macrophage and T cell          | embodiment of the invention             |
|     |         |     |               | chemotaxis are well known in the art    | includes a method for inhibiting (e.g., |
|     |         |     |               | and may be used or routinely            | reducing) MIP1a production. A           |
|     |         |     |               | modified to assess the ability of       | highly preferred indication is          |
|     |         |     |               | polypeptides of the invention           | infection (e.g., an infectious disease  |
|     |         |     |               | (including antibodies and agonists or   | as described below under "Infectious    |
|     |         |     |               | antagonists of the invention) to        | Disease"). Preferred indications        |
|     |         |     |               | mediate immunomodulation,               | include blood disorders (e.g., as       |
|     |         |     |               | modulate chemotaxis, and modulate       | described below under "Immune           |
|     |         |     |               | T cell differentiation. Exemplary       | Activity", "Blood-Related               |
|     |         |     |               | assays that test for                    | Disorders", and/or "Cardiovascular      |
|     |         |     |               | immunomodulatory proteins evaluate      | Disorders"). Highly preferred           |
|     |         |     |               | the production of chemokines, such      | indications include autoimmune          |
|     |         |     |               | as macrophage inflammatory protein      | diseases (e.g., rheumatoid arthritis,   |
|     |         |     |               | I alpha (MIP-1a), and the activation    | systemic lupus erythematosis,           |
|     |         |     |               | of monocytes/macrophages and T          | multiple sclerosis and/or as described  |
|     |         |     |               | cells. Such assays that may be used     | below) and immunodeficiencies (e.g.,    |
|     |         |     |               | or routinely modified to test           | as described below). Additional         |
|     |         |     |               | immunomodulatory and chemotaxis         | highly preferred indications include    |
|     |         |     |               | activity of polypeptides of the         | inflammation and inflammatory           |
|     |         |     |               | invention (including antibodies and     | disorders. Preferred indications        |
|     |         |     |               | agonists or antagonists of the          | also include anemia, pancytopenia,      |
|     |         |     |               | invention) include assays disclosed in  | leukopenia, thrombocytopenia,           |
|     |         |     |               | Miraglia et al., J Biomolecular         | Hodgkin's disease, acute                |
|     |         |     |               | Screening 4:193-204(1999);              | lymphocytic anemia (ALL),               |
|     |         |     |               | Rowland et al., "Lymphocytes: a         | plasmacytomas, multiple myeloma,        |
|     |         |     |               | practical approach" Chapter 6:138-      | Burkitt's lymphoma, arthritis, AIDS,    |
|     |         |     |               | 160 (2000); Satthaporn and Eremin, J    | granulomatous disease, inflammatory     |
|     |         |     |               | R Coll Surg Ednb 45(1):9-19 (2001);     | bowel disease, sepsis, neutropenia,     |
|     |         |     |               | Drakes et al., Transp Immunol           | neutrophilia, psoriasis, suppression    |
|     |         |     |               | 8(1):17-29 (2000); Verhasselt et al., J | of immune reactions to transplanted     |
|     |         |     |               | Immunol 158:2919-2925 (1997); and       | organs and tissues, hemophilia,         |

| representation, direless mellins, condocarditis, meninglis, Lyue blackers, sahma, and allery, Preferred indications and allery. Preferred indications also include morphosis diseases (e.g., lenkemin, prophora, and ros a deserble black was a  | A highly performed enhandment of the invention includes a method for in-hibiting (e.g., decreasing) TNF alpha production. An alternative highly perfected embodiment of the waterion includes a method for stimulating (e.g., increasing) TNF attention include (e.g., increasing) TNF attention include (e.g., increasing) TNF attention include blood disorders and appropriate of a sid escribed below under "Himmure Activity". "Blood-Related indications include blood disorders "and or "Cardiovascular Disorders", "Highly preferred indications include autorimment and include autorimment include autorimment include autorimment sichled autorimment sichled autorimment sichled autorimment of "On" signesse, etg., International orbitals, systemic lupus erythemutosis, systemic lupus erythemutosis, and/or as described below). |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Production of TINF alpha by dendrific cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 200                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSHAXZI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 203                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory   | in patients with rheumatory arthritism concerns and treating joint untangent indication is sepais. Highly preferred indication is include neoplastic diseases (e.g., leukemit, proprietred indications include neoplastic diseases (e.g., leukemit, proposition and described pelotion under Typerpositicative below under Typerpositicative below under Typerpositicative preferred indications include preferred indications include preferred indications, includent (e.g., malignant giftoms), agolitoms, and nonema, glitoms, and patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in patients, in and preserved indications of the malignary propositions, and for the patients in patients, and or hyperplass, an expedients, and or hyperplass, and preferred indications include amening parayopagenia, include amening parayopagenia, afterioris, AIDS, Burkti s'jumphoma, arthritis, AIDS, Burktis, propos                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| ra (TNFa), in opinion of an opinion of an opinion of an opinion of an opinion | minss or<br>stal, J<br>3-<br>3-<br>3-<br>proach"<br>nol<br>nol<br>manuol<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracleli<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>aracle<br>arac |
| tumor necrosis factor alpha () and the induction or imbibition inflammatory or eyoloxic res Such assays that may be used routinely modified to test immunomodilatory activity or polypeptides of the invention                | unaugoniss of the twenton) in anagoniss of the twenton) in snawy debicshood in Murglin et al. 204(1992) Rowland et al., 204(1992) Rowland et al., 204(1992) Rowland et al., 204(1992) Rowland et al., 204(200), Verhasselt et al., Enr I Immun 204(1) 2886-2890 (11987, Pal al., 1 Immunol 160(7),2852-38 (1988), Verhasselt et al., 1 Im 1822919-2925 (1998), the contents of each of an al., 1 Leukee Biol 66 822-48 (1998), the contents of each of an electric him non-protected by refer in some deedful in seaturey. Human dendrift that may be used according to assays may be used according to techniques disclosed herein or otherwise known in the art. He dendrift cells are antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen present antigen and unregain activities.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| cwample, melanoma, rental cell actionaria, lottalenia, jumpiona, and prostate, bestaf, intag, coton. brain, liver and trimary cancer. Other brain, liver and trimary cancer. Other perferred indications include benign dysponifications include benign dysponifications include benign dysponifications include benign dysponifications, such as, for example, hyperplasia, metaplasia, pancystoperaia, lettoperaia, disease, acute lymphocytic ancent mycloma, Burkitz is lymphoma, adisease, incurporain, enterophilia, psociases, hemophilia, psociases, hemophilia, psociases, hemophilia, psociases, hemophilia, psociases, perception, diseases, endoceutilis, meningitis, Lyme Diseases, suppression of immume endones of mensplanted organs, staffina and allergy. | the highly preferred indication is in the place seem than 5 and additional highly preferred indication is a complication season expiration of a seem of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place of the place |
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| WH (1999), the contents of each of which are better in compound by reference in its entirety. Exemplary man T cells, search site the MOLT-4, that may be used according to these assays are publicly available (e.g., through the ATCCT-1).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polyperpides of the invention (meltaling ambodies of the invention (meltaling ambodies of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by HMAT issing anti-art insulin antibodies. In this inservation from pancreatic bed and the secretion of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the contro |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| blood vessel blooks as heart disease | otoou reset monage, near mease,     | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and       | disorders as described in the      | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine   | disorders (as described in the      | "Endocrine Disorders" section       | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious  | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's      | contracture). An additional        | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. Additional | highly preferred indications are   | complications associated with insulin | resistance.                       |                                 |                                    |                                   |                                 |
| bue soliton/aniotom metalia ha vale  | also of certain process peaces, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodics and agonists or | antagonists of the invention) include | assays disclosed in: Shimizu, H., et | al., Endocr J, 47(3):261-9 (2000); | Salapatck, A.M., ct al., Mol       | Endocrinol, 13(8):1305-17 (1999); | Filipsson, K., et al., Ann N Y Acad | Sci, 865:441-4 (1998); Olson, L.K., | et al., J Biol Chem, 271(28):16544- | 52 (1996); and, Miraglia S ct. al.,    | Journal of Biomolecular Screening,  | 4:193-204 (1999), the contents of   | each of which is herein incorporated | by reference in its entirety. | Pancreatic cells that may be used   | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary pancreatic cells that may    | be used according to these assays    | include HITT15 Cells. HITT15 are     | an adherent epithelial cell line   | established from Syrian hamster islet  | cells transformed with SV40. These | cells express glucagon, somatostatin, | and glucocorticoid receptors. The | cells secrete insulin, which is | stimulated by glucose and glucagon | and suppressed by somatostatin or | glucocorticoids. ATTC# CRL-1777 |
|                                      |                                     |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                      |                                    |                                    |                                   |                                     |                                     |                                     |                                        |                                     |                                     |                                      |                               |                                     |                                        |                                      |                                    |                                        |                                      |                                      |                                    |                                        |                                    |                                       |                                   |                                 |                                    |                                   |                                 |
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|                                                                                                                             | invention include using polyptides of the invention include using polyptides of the invention (or antibodies, protestion, and or treatment or Neurological and or treatment or Neurological Diseases and Diseases, Parkinson's Disease, Bain Cancer, Sefarres).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Refs: Lord and Ashcroft. Biochem.<br>J. 219: 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | transcription through the NFB response clement are well-known in the response clement are well-known in the response clement are well-known in modified to sussess the ability of popperables of the invention to the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention of the invention include and sognet death of the invention include on the invention of the invention of the invention of the invention of the invention include and separable sand agonts as of the invention include and angents death-off of (1998); Called and Malm, Methods in Enzymol Malm, Methods in Enzymol Aramburan et al., 15 etc. 66:14 (1998); Uller and Malm, Methods in Enzymol Proc Natl Acad Sci Ulles & Sci Sci Sci Sci Sci Sci Sci Sci Sci Sci |
|                                                                                                                             | Activation of Transarpition through NFKB response element in neuronal cells (such as SKNMC cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                             | 809                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| used according to these reasons are publicly severable (cells that may be according to these reasons are publicly available (e.g., through the cells (cells, cells, | Rismae seasy. Kinese seasy, for creamping and the company of the first signal transduction that regulate company of profitereating and propriet of the remainding adipocyte profitereating and propriets of the remainding adipocyte profitereating and the remainding a profitereating and the remainding a profitereating and the remainding a properties of the mention in promote or inhibit of polypeptides of the mention in promote or inhibit of polypeptides of the mention in promote or inhibit of polypeptides of the mention in the remainding and profiterent and the profiterent of the invention in the remainding and profitered and a quality of profitered and a profiterent or inhibit of propriets of the invention includes a method for inhibiting and profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a quality of profitered and a qual |
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| entirety. Ner used according publicity avail ATCC <sup>(NA)</sup> , E that may be u assays includ cell line.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Activation of Kimase assay, Kimese assay, Kimese assay, Kimese Signaling Pathway Caumple in Tile Liknase and proliferation of difficulty and are well fashway in the art well fashway in the art well fashway in the art well fashway in the ability of polyperplace of rounding-by modificulties and architecturion in promote or proliferation, activation, acti |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSJBQ79 609                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| "Hyperproliferative Disorders").     | Preferred indications include blood | disorders (e.g., hypertension,       | congestive heart failure, blood vessel      | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, |
| entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCC <sup>TM</sup> ). Exemplary | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |
|                                      |                                     |                                      |                                             |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |
|                                      |                                     |                                      |                                             |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           | _                                    |
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|  | stroke, and other diseases and          |
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|  | disorders as described in the           |
|  | "Cardiovascular Disorders" section      |
|  | below), dyslipidemia, endocrine         |
|  | disorders (as described in the          |
|  | "Endocrine Disorders" section           |
|  | below), neuropathy, vision              |
|  | impairment (e.g., diabetic retinopathy  |
|  | and blindness), ulcers and impaired     |
|  | wound healing, infection (e.g.,         |
|  | infectious diseases and disorders as    |
|  | described in the "Infectious            |
|  | Diseases" section below (particularly   |
|  | of the urinary tract and skin). An      |
|  | additional highly preferred indication  |
|  | is obesity and/or complications         |
|  | associated with obesity. Additional     |
|  | highly preferred indications include    |
|  | weight loss or alternatively, weight    |
|  | gain. Additional highly                 |
|  | preferred indications are               |
|  | complications associated with insulin   |
|  | resistance. Additional highly           |
|  | preferred indications are disorders of  |
|  | the musculoskeletal systems             |
|  | including myopathies, muscular          |
|  | ξ,                                      |
|  | herein. Additional highly               |
|  | preferred indications include,          |
|  | hypertension, coronary artery           |
|  | disease, dyslipidemia, gallstones,      |
|  | osteoarthritis, degenerative arthritis, |
|  | eating disorders, fibrosis, cachexia,   |
|  | and kidney diseases or disorders.       |
|  | Preferred indications include           |
|  | neoplasms and cancer, such as,          |
|  | lymphoma, leukemia and breast,          |

| colon, and kidney emeer. Additional perferred indications include melanoma, prostate, lung metaretti, colonical series discussions in the protection, cospolage al, someth, liver, and trimary cancer. Highly preferred indications include lipomas and jitosateomas. Other preferred indications include benign dependent of the proposition of the proposition of the proposition of the propositions, such as, for example, hyporalisas, metaplisas, and and or dysplasia. | A highly preferred emboliment<br>of the invention includes a method<br>of seaminaing the production of<br>GM-CSE. An alternative highly<br>perferred emboliment of the<br>invention includes a method for<br>including the production of GM-<br>cSE. Highly preferred indications<br>include afficient highly preferred indications<br>include afficient highly preferred indication<br>influmnator of democracy in includes<br>influence of the preferred indication<br>influence of the preferred indication<br>influence of the preferred indications include<br>the preferred indications include<br>blood disorders (e.g., neutropenia<br>(e.g., in HV infected patients),<br>and the prevention of neutropenia<br>(e.g., in HV infected patients),<br>products, and or a described below under<br>"Immune Akrvity", "Blood-Related<br>Disorders," and confluence under<br>diseases (e.g., rheumatoid arthritis,<br>preferred diseases (e.g., rheumatoid arthritis,<br>preferred authorities of preferred<br>diseases (e.g., rheumatoid arthritis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | expressed by activated Teelts, and workers FMAT. CMA-CSF is according to the commorphages, concluding the commorphages concluding the commorphage concluding the commorphage commorphage manulocytes macrophage and according the color of the commorphage and the commorphage and the commorphage and the commorphage and the commorphage and monophage and monophage and monophage and the clifferentiation of the commorphage and monophage and procentarion. GMA-CSF pages and procentarion. GMA-CSF is considered to be a point immunomediatory proceins that promitted monthly modified to assess well known in the anti so of polyperidies of the invention (moduling authorities and invention) to noctiate and inferentiation of the invention to noctiate and entitle of polyperidies of the invention to noctiate and modulate the invention to noctiate and modulate the growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and differentiation of growth and different an |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Production of GM-CSF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HSKDA27                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 206                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| below) and immunodeficiencies (e.g.,<br>ascariede dolow). Additional<br>highly preferred indications include<br>and any preferred indications include<br>and any preferred indications include<br>indications include neoplastic<br>diseases (e.g., lenkemia (e.g., acute<br>prophobistic (externia, and acute<br>myologanous (enkemia), pumptoma<br>myologanous (enkemia), pumptoma<br>Hodgisti's disease), and/or as<br>exceptube lolew unider re-<br>-Hyoromanificentive. Diseasee,                                                                                                                                              | the preferred indications include neoplisarus and cancers, such as neoplisarus and cancers, such as the defencia Lymphoura, mediumora, and prostate, bresel, lung, colon, provereite, escoplisaguel, stormet, predirectie, escoplisaguel, stormet, preferred indications include benign proprietative discueders and presente, luperpulsaria, menghasia, menghasia, andro dysplasia, menghasia, andro dysplasia, Highly preferred indications indicate suppression of immune reactions to transplanted                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | transplant), accelerating myeloid recovery, and mobilizing weeloid myeloid recovery, and mobilizing herangopicite progenior cells. Preferred indications include Preferred indications include response, and alternatively. Tell-Incidiated immune response, and alternatively immune response, Preferred indications include anemia indications include anemia indications include anemia, indications include anemia, thrombocytopenia, active permanent indications include anemia, thrombocytopenia, active |
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| leukocytes. Exemplary assays that acts for immunoculatory proteins evaluate the production of cytokines, as as GW-CR5, and the activation of T cells. Such assays that many be used or routinely modified to test immunoculatory activity of polypeptides of the invention polypeptides of the invention analysis of the invention including amploties and agonists or analysomist of the invention included analyses of the invention included analyses of the invention include analyses of the invention include analyses of the invention include analyses of the invention include analyses of the invention include analyses. | Act (1999); Rowland et al., "Lymphocytes: a practical approach"  "Lymphocytes: a practical approach"  al., I Lenkoe Biol (88Q,215-233,  al., I Lenkoe Biol (88Q,215-233,  al., I Lenkoe Biol (88Q,215-233,  al., I Lenkoe Biol (88Q,215-233)  in the countries of each o'vidule are been inconversared by reference in  its entirety. Natural feller cells that  is entirety. Natural feller cells that  is entirety. Natural feller cells that  is entirety. Natural feller cells that  in the countries of countries of the cells are  assays are publicly available (e.g.,  insupplied (e.g.,  assays are publicly available (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  salanda (e.g.,  saland | avanular lympotaet that have eyotooxis eativity but do bind antigen. NK cells show anthody-independent killing of tumor cells and slas recognize authody bound on target cells, via NK Fe receptors, leading to cell-mediated cytotoxicity.                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

| HSKGN81 611 |
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|     |         |     |               | also by certain proteins/nentides and   | blood vessel blockage heart disease    |
|-----|---------|-----|---------------|-----------------------------------------|----------------------------------------|
|     |         |     |               | disneonlation is a key component in     | stroke imnotence (e.g. due to          |
|     |         |     |               | diabetes. Exemplary assays that may     | diabetic neuropathy or blood vessel    |
|     |         |     |               | be used or routinely modified to test   | blockage), seizures, mental            |
|     |         |     |               | for stimulation of insulin secretion    | confusion, drowsiness, nonketotic      |
|     |         |     |               | (from pancreatic cells) by              | hyperglycemic-hyperosmolar coma,       |
|     |         |     |               | polypeptides of the invention           | cardiovascular disease (e.g., heart    |
|     |         |     |               | (including antibodics and agonists or   | disease, atherosclerosis,              |
|     |         |     |               | antagonists of the invention) include   | microvascular disease, hypertension,   |
|     |         |     |               | assays disclosed in: Ahren, B., et al., | stroke, and other diseases and         |
|     |         |     |               | Am J Physiol, 277(4 Pt 2):R959-66       | disorders as described in the          |
|     |         |     |               | (1999); Li, M., ct al., Endocrinology,  | "Cardiovascular Disorders" section     |
|     |         |     |               | 138(9):3735-40 (1997); Kim, K.H.,       | below), dyslipidemia, endocrine        |
|     |         |     |               | et al., FEBS Lett, 377(2):237-9         | disorders (as described in the         |
|     |         |     |               | (1995); and, Miraglia S ct. al.,        | "Endocrine Disorders" section          |
|     |         |     |               | Journal of Biomolecular Screening,      | below), neuropathy, vision             |
|     |         |     |               | 4:193-204 (1999), the contents of       | impairment (e.g., diabetic retinopathy |
|     |         |     |               | each of which is herein incorporated    | and blindness), ulcers and impaired    |
|     |         |     |               | by reference in its entirety.           | wound healing, and infection (e.g.,    |
|     |         |     |               | Pancreatic cells that may be used       | infectious diseases and disorders as   |
|     |         |     |               | according to these assays are publicly  | described in the "Infectious           |
|     |         |     |               | available (e.g., through the ATCCTM)    | Diseases" section below, especially    |
|     |         |     |               | and/or may be routinely generated.      | of the urinary tract and skin), carpal |
|     |         |     |               | Exemplary pancreatic cells that may     | tunnel syndrome and Dupuytren's        |
|     |         |     |               | be used according to these assays       | contracture). An additional            |
|     |         |     |               | include rat INS-1 cells. INS-1 cells    | highly preferred indication is obesity |
|     |         |     |               | are a semi-adherent cell line           | and/or complications associated with   |
|     |         |     |               | established from cells isolated from    | obesity. Additional highly preferred   |
|     |         |     |               | an X-ray induced rat transplantable     | indications include weight loss or     |
|     |         |     |               | insulinoma. These cells retain          | alternatively, weight gain.            |
|     |         |     |               | characteristics typical of native       | Aditional highly preferred             |
|     |         |     |               | pancreatic beta cells including         | indications are complications          |
|     |         |     |               | glucose inducible insulin secretion.    | associated with insulin resistance.    |
|     |         |     |               | References: Asfari et al.               |                                        |
|     |         |     |               | Endocrinology 1992 130:167.             |                                        |
|     | HSKNB56 | 612 | Activation of | Kinase assay. Kinase assays, for        | A highly preferred embodiment          |
| 208 |         |     | Adipocyte ERK | example an Elk-1 kinase assay, for      | of the invention includes a method     |

| Signaling Pathway  Elik Signal transduction that regulated cold profileration or differentiation are well known in the at and may be a cold profileration modified to assess the ability of polypepuldes of the ability of polypepuldes of the ability of polypepuldes of the ability of polypepuldes of the ability of polypepuldes of the ability of an attachmic and against or attachmic and provideration, activation, and against of the ability of polypepuldes of the ability of the polypepuldes of the invention of including ambidicis and sponsis or routinely modified to sea SPR Kinase-attached activity of a constitution, activation, and condition and activation of polypepuldes of the invention (including ambidicis and sponsis or antigonisis of the invention) include the assyst sideodes in Forter et al., Biol Chem 379(8-9):101-1110 (1998); Le Manhand-Hausel Y. Esp. Clin Endocrinol Diabects  Clin Endocrinol Diabects  High Programma and Karin Nature  410(682-1377-40 (2001); and Cosb Mill, Prog Bordys Mol Biol 11(3-4)75-30 (1909); the contents of each of which in the levent in incorporated by reference in the order of which in the beetin in the order of the programma of the contents of each of which in the beetin in the order of the programma of the seasons are publishe waithhole (e.g., assays are publishe you alloads of the contents of the decorating to these assays include 373-141. It is a the content of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the co |
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| 3T3 fibroblast cells developed       | disorders (e.g., as described below    |
|--------------------------------------|----------------------------------------|
| through clonal isolation and undergo | under "Immune Activity"), neural       |
| a pre-adipocyte to adipose-like      | disorders (e.g., as described below    |
| conversion under appropriate         | under "Neural Activity and             |
| differentiation conditions known in  | Neurological Diseases"), and           |
| the art.                             | infection (e.g., as described below    |
|                                      | under "Infectious Disease").           |
|                                      | A highly preferred indication is       |
|                                      | diabetes mellitus. An additional       |
|                                      | highly preferred indication is a       |
|                                      | complication associated with           |
|                                      | diabetes (e.g., diabetic retinopathy,  |
|                                      | diabetic nephropathy, kidney disease   |
|                                      | (e.g., renal failure, nephropathy      |
|                                      | and/or other diseases and disorders as |
|                                      | described in the "Renal Disorders"     |
|                                      | section below), diabetic neuropathy,   |
|                                      | nerve disease and nerve damage         |
|                                      | (e.g., due to diabetic neuropathy),    |
|                                      | blood vessel blockage, heart disease,  |
|                                      | stroke, impotence (e.g., due to        |
|                                      | diabetic neuropathy or blood vessel    |
|                                      | blockage), seizures, mental            |
|                                      | confusion, drowsiness, nonketotic      |
|                                      | hyperglycemic-hyperosmolar coma,       |
|                                      | cardiovascular disease (e.g., heart    |
|                                      | disease, atherosclerosis,              |
|                                      | microvascular disease, hypertension,   |
|                                      | stroke, and other diseases and         |
|                                      | disorders as described in the          |
|                                      | "Cardiovascular Disorders" section     |
|                                      | below), dyslipidemia, endocrine        |
|                                      | disorders (as described in the         |
|                                      | "Endocrine Disorders" section          |
|                                      | below), neuropathy, vision             |
|                                      | impairment (e.g., diabetic retinopathy |
|                                      | and blindness), ulcers and impaired    |

|  |   | wound healing infection (e.g.           |
|--|---|-----------------------------------------|
|  |   | infections discovery and discussion on  |
|  |   | miectious diseases and disorders as     |
|  | 3 | described in the injections             |
|  |   | Diseases" section below (particularly   |
|  |   | of the urinary tract and skin). An      |
|  |   | additional highly preferred indication  |
|  |   | is obesity and/or complications         |
|  |   | associated with obesity. Additional     |
|  |   | highly preferred indications include    |
|  |   | weight loss or alternatively, weight    |
|  | - | gain. Additional highly                 |
|  |   | preferred indications are               |
|  |   | complications associated with insulin   |
|  | 1 | resistance. Additional highly           |
|  |   | preferred indications are disorders of  |
|  |   | the musculoskeletal systems             |
|  |   | including myopathies, muscular          |
|  |   | dystrophy, and/or as described          |
|  |   | herein. Additional highly               |
|  | I | preferred indications include,          |
|  | 1 | hypertension, coronary artery           |
|  |   | disease, dyslipidemia, gallstones,      |
|  |   | osteoarthritis, degenerative arthritis, |
|  |   | eating disorders, fibrosis, cachexia,   |
|  |   | and kidney diseases or disorders.       |
|  |   | Preferred indications include           |
|  | 1 | neoplasms and cancer, such as,          |
|  | _ | lymphoma, leukemia and breast,          |
|  |   | colon, and kidney cancer. Additional    |
|  | I | preferred indications include           |
|  | 1 | melanoma, prostate, lung,               |
|  | I | pancreatic, esophageal, stomach,        |
|  |   | brain, liver, and urinary cancer.       |
|  |   | Highly preferred indications include    |
|  |   | lipomas and liposarcomas. Other         |
|  |   | preferred indications include benign    |
|  | 9 | dysproliferative disorders and pre-     |

| neoplastic conditions, such as, for example, hyperplasta, metaplasia, and/or dysplasia. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                                                                         | installin are well-known in the art and missilin are well-known in the art and assess the ability of polypyrides of the invention to hotherize an analysis of the invention to submitted problems of the invention of the properties of the invention of submitted problems of the invention of submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or submitted or sub |
|                                                                                         | Sciential Simulation of insulin secretion from paracratic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                         | 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                         | HSNAD72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                         | 500                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| the turnor was and ship, to any alternate synchrone and Daphytten's controcture. An an additional and a specification and additional and a confine and a sesciented with beighty preferred indications associated with obesity. Additional highly preferred indications and take weight associated with the additional highly preferred indications are complications are complications as associated with insulin resistance.                                                      | A highly preferred indication is diabetes multius. An additional highly preferred indication is a complication associated with diabetes (e.g. clainedic retinopathy, diabetes (e.g. clainedic retinopathy, diabetes (e.g. clainedic retinopathy, diabetes (e.g. clainedic retinopathy, diabetes (e.g. clainedic retinopathy, diabetes (e.g. clainedic retinopathy and or other diseases and disonders such or clained in the "Realal Disorders" successible in the "Realal Disorders" successible in the "Realal Disorders" successible in the "Realal Disorders" successible of e.g. due to diabetic neuropathy, blood vessel blockage, heart disease, admost composition, downsess, nonketotic hypergly-centic-lip-personal-retinosity control seases, claines, in preference of physical collision, downsess, nonketotic hypergly-centic-lip-personal-resolution, downsess, and diseases, and dother diseases and diseases and dother diseases and effectives and collision developed in season and collision developed in the clained "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Cardiovascaliter Disorders" section of "Car |
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| Exemplary pearcracid cells that may be used may be tourished generated. The used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line are a semi-adherent cell line catablished from cell isolated from in X-ray induced rat transplantable and a semi-adherent cells including the cells including characteric step yiel of marker glaucose inducible insulin secretion glaucose inducible insulin secretion. He deferences: Ashiri et al. | Assays for measuring eachigm flux are well-known in the art and may be well-known in the art and may be add or rounding to medical to assess the shilty of polypopides of the inversation (including authodics and agonists or autagonists of the mercition) to mobilize calcium. For orangie, the FIPR assay may be used to measure influx of calcium. For assay may be used to measure influx of calcium connecutrations of cytosolic calcium connecutrations of cytosolic calcium connecutrations of cytosolic calcium connecutrations of calcium. Extracellular calcium, Extracellular calcium, Extracellular calcium, Extracellular calcium, Extracellular calcium, Extracellular calcium, Extracellular calcium is calcular to calcium responsive signaling publivays and attentions in cell functions. Exemplary assays that may be used or nontimely modified to measure calcium flux by measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux by in measure calcium flux |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Simulation of Calcium<br>Plux in peacreatic beta<br>cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>614</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HSNMC45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 210                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| 615 Simulation of insulin secretion from pararreatic beta cells. |
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|                                                                  |

| described in the "Renal Disorders" | section below), diabetic neuropathy, |                                        | (e.g., due to diabetic neuropathy), | _                                      | stroke, impotence (e.g., due to     | iy diabetic neuropathy or blood vessel | t   blockage), seizures, mental       | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | ÷                                     | e microvascular disease, hypertension, | , stroke, and other diseases and        | disorders as described in the     | y, Cardiovascular Disorders" section   | below), dyslipidemia, endocrine   | _                               | "Endocrine Disorders" section    | below), neuropathy, vision         | _                                 | _                                    | wound healing, and infection (e.g., | infectious diseases and disorders as | _                                      | _                                    |                                    | tunnel syndrome a                   | Ť                                 | highly preferred indication is obesity |                               | Ť                                    | indications include weight loss or  | alternatively, weight gain.    | Aditional highly preferred        | indications are complications   | associated with insulin resistance.  |
|------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------------|-----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|------------------------------------|-------------------------------------|-----------------------------------|----------------------------------------|-------------------------------|--------------------------------------|-------------------------------------|--------------------------------|-----------------------------------|---------------------------------|--------------------------------------|
| secretion is measured by FMAT      | using anti-rat insulin antibodies.   | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may    | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include  | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S ct. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | are a semi-adherent cell line | established from cells isolated from | an X-ray induced rat transplantable | insulinoma. These cells retain | characteristics typical of native | pancreatic beta cells including | glucose inducible insulin secretion, |
| _                                  |                                      |                                        |                                     |                                        |                                     |                                        |                                       |                                      |                                  |                                     |                                       |                                        |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                   |                                      |                                     |                                      |                                        |                                      |                                    |                                     |                                   |                                        |                               |                                      |                                     |                                |                                   |                                 |                                      |
|                                    |                                      |                                        |                                     |                                        |                                     |                                        |                                       |                                      |                                  |                                     |                                       |                                        |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                   |                                      |                                     |                                      |                                        |                                      |                                    |                                     |                                   |                                        |                               |                                      |                                     |                                |                                   |                                 |                                      |

|                                                          | indication is<br>An                                           | red indication                                                              | retinopathy,                          | idney disease                        | ıropathy                              | nd disorders as                        | Disorders"                                                               | damage,                           | uropathy),                          | heart disease,                        | due to                           | blood vessel                        | ntal                          | nonketotic                           | molar coma,                      | (e.g., heart                        |                                       | hypertension,                        | es and                              | n the                               | lers" section                      | ndocrine                               | in the                                | section                       | sion                              | tic retinopathy                        | nd impaired                          | fection (e.g.,                       | disorders as                         | ious                            | v, especially                         | skin), carpal                          |
|----------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------------------------------------------|-----------------------------------|-------------------------------------|---------------------------------------|----------------------------------|-------------------------------------|-------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|---------------------------------------|-------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|---------------------------------|---------------------------------------|----------------------------------------|
|                                                          | A highly preferred indication is<br>diabetes mellitus. An     | additional highly preferred indication<br>is a complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy     | and/or other diseases and disorders as | described in the "Kenal Disorders"<br>section below) disbetic neuronarby | nerve disease and nerve damage    | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to  | diabetic neuropathy or blood vessel | blockage), seizures, mental   | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension, | stroke, and other diseases and      | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine        | disorders (as described in the        | "Endocrine Disorders" section | below), neuropathy, vision        | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g.,  | infectious diseases and disorders as | described in the "Infectious    | Diseases" section below, especially   | of the urinary tract and skin), carpal |
| References: Asfari et al.<br>Endocrinology 1992 130:167. | Assays for the regulation of<br>transcription through the FAS | promoter element are well-known in<br>the art and may be used or routinely  | modified to assess the ability of     | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) to       | activate the FAS promoter element in                                     | transcription of FAS a key enzyme | for lipogenesis. FAS promoter is    | regulated by many transcription       | factors including SREBP. Insulin | increases FAS gene transcription in | livers of diabetic mice. This | stimulation of transcription is also | somewhat glucose dependent.      | Exemplary assays that may be used   | or routinely modified to test for FAS | promoter element activity (in        | hepatocytes) by polypeptides of the | invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed in | Xiong, S., et al., Proc Natl Acad Sci | U.S.A., 97(8):3948-53 (2000); | Roder, K., et al., Eur J Biochem, | 260(3):743-51 (1999); Oskouian B,      | et al., Biochem J, 317 (Pt 1):257-65 | (1996); Berger, et al., Gene 66:1-10 | (1988); and, Cullen, B., et al.,     | Methods in Enzymol. 216:362-368 | (1992), the contents of each of which | is herein incorporated by reference in |
|                                                          | Regulation of<br>transcription through                        | the FAS promoter<br>element in henatocytes                                  |                                       |                                      |                                       |                                        |                                                                          |                                   |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                      |                                      |                                      |                                 |                                       |                                        |
|                                                          | 919                                                           |                                                                             |                                       |                                      |                                       |                                        |                                                                          |                                   |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                      |                                      |                                      |                                 |                                       |                                        |
|                                                          | HSRFZ57                                                       |                                                                             |                                       |                                      |                                       |                                        |                                                                          |                                   |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                      |                                      |                                      |                                 |                                       |                                        |
|                                                          | 212                                                           |                                                                             |                                       |                                      |                                       |                                        |                                                                          |                                   |                                     |                                       |                                  |                                     |                               |                                      |                                  |                                     |                                       |                                      |                                     |                                     |                                    |                                        |                                       |                               |                                   |                                        |                                      |                                      |                                      |                                 |                                       |                                        |

|     |         |     |                      | its entirety. Hepatocytes that may be used according to these assays, such as HHE cells, are publicly available (e.g., through the ATCCTM) and/or | tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with |
|-----|---------|-----|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
|     |         |     |                      | may be routinely generated.  Exemplary hepatocytes that may be                                                                                    | obesity. Additional highly preferred<br>indications include weight loss or                                                              |
|     |         |     |                      | used according to these assays                                                                                                                    | alternatively, weight gain.                                                                                                             |
|     |         |     |                      | include rat liver hepatoma cell line(s)<br>inducible with glucocorticoids.                                                                        | Aditional highly preferred<br>indications are complications                                                                             |
|     |         |     |                      | insulin, or cAMP derivatives.                                                                                                                     | associated with insulin resistance.                                                                                                     |
|     | HSRFZ57 | 616 | Production of VCAM   | Assays for measuring expression of                                                                                                                | Highly preferred indications include                                                                                                    |
| 212 |         |     | in endothelial cells | VCAM are well-known in the art and                                                                                                                | inflammation (acute and chronic),                                                                                                       |
|     |         |     | (such as human       | may be used or routinely modified to                                                                                                              | restnosis, atheroselerosis, asthma and                                                                                                  |
|     |         |     | umbilical vein       | assess the ability of polypeptides of                                                                                                             | allergy. Highly preferred indications                                                                                                   |
|     |         |     | CHIOOLICIIAI CCIIS   | and agonists or antagonists of the                                                                                                                | include illustrituation and<br>inflammatory disorders                                                                                   |
|     |         |     | ((271.011)           | invention) to regulate VCAM                                                                                                                       | immunological disorders neonlastic                                                                                                      |
|     |         |     |                      | expression. For example, FMAT                                                                                                                     | disorders (e.g. cancer/tumorigenesis),                                                                                                  |
|     |         |     |                      | may be used to meaure the                                                                                                                         | and cardiovascular disorders (such as                                                                                                   |
|     |         |     |                      | upregulation of cell surface VCAM-1                                                                                                               | described below under "Immune                                                                                                           |
|     |         |     |                      | expresssion in endothelial cells.                                                                                                                 | Activity", "Blood-Related                                                                                                               |
|     |         |     |                      | Endothelial cells are cells that line                                                                                                             | Disorders", "Hyperproliferative                                                                                                         |
|     |         |     |                      | blood vessels, and are involved in                                                                                                                | Disorders" and/or "Cardiovascular                                                                                                       |
|     |         |     |                      | functions that include, but are not                                                                                                               | Disorders"). Highly preferred                                                                                                           |
|     |         |     |                      | limited to, angiogenesis, vascular                                                                                                                | indications include neoplasms and                                                                                                       |
|     |         |     |                      | permeability, vascular tone, and                                                                                                                  | cancers such as, for example,                                                                                                           |
|     |         |     |                      | immune cell extravasation.                                                                                                                        | leukemia, lymphoma, melanoma,                                                                                                           |
|     |         |     |                      | Exemplary endothelial cells that may                                                                                                              | renal cell carcinoma, and prostate,                                                                                                     |
|     |         |     |                      | be used according to these assays                                                                                                                 | breast, lung, colon, pancreatic,                                                                                                        |
|     |         |     |                      | include human umbilical vein                                                                                                                      | esophageal, stomach, brain, liver and                                                                                                   |
|     |         |     |                      | endothelial cells (HUVEC), which                                                                                                                  | urinary cancer. Other preferred                                                                                                         |
|     |         |     |                      | are available from commercial                                                                                                                     | indications include benign                                                                                                              |
|     |         |     |                      | sources. The expression of VCAM                                                                                                                   | dysproliferative disorders and pre-                                                                                                     |
|     |         |     |                      | (CD106), a membrane-associated                                                                                                                    | neoplastic conditions, such as, for                                                                                                     |
|     |         |     |                      | protein, can be upregulated by                                                                                                                    | example, hyperplasia, metaplasia,                                                                                                       |
|     |         |     |                      | cytokines or other factors, and                                                                                                                   | and/or dysplasia.                                                                                                                       |
|     |         |     |                      | contributes to the extravasation of                                                                                                               |                                                                                                                                         |

| ther<br>els;<br>i role                                                                                                                               | A highly preferred indication is additional highly preferred indication in the set complication associated with distorts (e.g., disheit retinopathy, and with dishects (e.g., disheit retinopathy, and with disheit capabilation). The section below, disheit in employably many care in described in the Feath Bloorders' and andro other disheit emorphity, and section below, disheit emorphity, and section below, disheit emorphity, and section below, disheit emorphity, and section below, disheit emorphity, blood vessel bloods, sectors, needs, sectors, many complished, and section below, disheit emorphity or blood vessel bloods, sectors, mental condision, diswisses, nonlissen, diswisses, preferration, study diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen, diswisses, nonlissen |
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| lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses. | gh<br>gress                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                      | Keglutian of Regulation of Regulation of Respective through the FAS promoter element in hepatocytes (element in hepatocytes).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                      | HSUBW09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| described in #- infectional Diseases' section below, especially of or the urinary ror and sistin, carple tunnel syndrome and Disputerial tunnel syndrome and Disputerial tunnel syndrome and Disputerial tunnel syndrome and roc countectury.  An additional lighty preferred indication is obesity and for complications associated with indications are complicational lighty preferred indications and the weight loss or indications are complications.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred faithcast mellitus. An additional highly preferred faithcast mellitus. An additional is disbects mellitus. An indication is disbects mellitus. An |
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| Andreakes in European, 216:52-368<br>(1992), the contents of each of which<br>herein incorporated by reference in<br>its entirety. Hepatocytes that may be<br>used according to these assays, such<br>used according to these assays, such<br>as IHIII cells, my publicly ornithel<br>Ce.g., through the ATCC <sup>19</sup> andror<br>and the content of the property of the<br>Exemplary hepatocytes that may be<br>include and these assays<br>include and these assays<br>include and these bases<br>include and these bases of<br>include and these themona cell line(s)<br>include and thousand cell line(s)<br>include and these themona cell line(s)<br>include and these assays include and the control of the<br>include and the control of the control of the<br>include and the control of the control of the<br>include and the control of the control of the control of the<br>include and the control of the control of the control of the<br>include and the control of the control of the control of the<br>include and the control of the control of the control of the<br>include and the control of the control of the control of the<br>include of the control of the control of the control of the control of the<br>include of the control of the control of the control of the control of the<br>include of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of | regulatory and coding sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence of sequence | Assays for the activation of transcription through the cAMP irresponse element are well-known in the art and may be used or routinely modified to assess the ability of polypepties of the invention of polypepties of the invention (including antibodies and agoniss or                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | This is a squalence synthesis or square synthesis or contract transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Activation of<br>transcription through<br>cAMP response<br>element (CRE) in pre-<br>adipocytes.                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 617                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 618                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HSUBW09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HSVBU91                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 213                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 214                                                                                                                                                                                                                                                                                                                                                                |

| resistance.                                                                                                                                                                                                                                                                                                                                                                                                                   | A highly perfected enhodiment of the invention includes a machod for aminating hepotocyte cell politication. An alternative highly perfected enhodiment of the invention includes a method for minimiting bengavoir cell politication. A highly proferred enhodiment of the invention includes a method for including the profession of the invention includes a method for simulating hepatocyte cell differentiation. An alternative highly proferred enhodiment of the invention includes a method for influing hepatocyte cell differentiation. An authorities a method for influing hepatocyte cell differentiation. An alternative highly preferred enhodiment of the invention includes a method for influinting the invention includes a method for influinting the distribution of additional profession of the invention includes a method for influinting the stretching of perfect intervition of methods in endevined structure of the invention includes a method for influinting the substitution of addition includes a method for influinting the substitution of addition includes a method for influinting the invention includes a method for influinting the invention of addition includes in method with alternative lightly preferred instruction of addition included struction of additional included struction of additional included struction of additional included struction of additional included struction of additional included struction of additional included struction of additional included struction of additional included structio |
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| that may be used according to these<br>seasy include 371-L1 (eds.) 371-L1 is an adherent mouse preadpoorte<br>in the seasy include 371-L1 (eds.) 371-L1 is an adherent mouse preadpoorte<br>of 3713 fibroblass cells developed<br>through clonal isolation and undergo a<br>preadpoorte on adipose-like<br>conversion under appropriate<br>on westion under appropriate<br>the first metalion conditions known in<br>the art. | coumple an Eller Itimus easays, for exumple an Eller Itimus easays, for the Re again transpaction that regulate cell poulieration or differentiation cell poulieration or differentiation even bloom in the act and may be used or reminely modified to assess the ability of rophypridies of the invention (including ambodies and agonists or antagoniss of the invention) to promote or inhibit cell invention) to promote or inhibit cell invention) to promote or inhibit cell invention, activation as easays for ERK kinase activity that may be used differentiation. Exemplay assays for ERK kinase activity that may be used to cuminally modified to test ERK kinase activity that may be used to cuminally modified to test ERK kinase activity that may be used to cuminally modified to test ERK kinase activity that may be used to cuminally modified to test ERK kinase activity that may be agoniss or amagoniss of the invention included the through soft and the commission of the invention of the says of schooled in Forter et al. (1998); kyvitakis JM, Biochem Soc 2010; and Cobb MI, Prog Biophys, Mol Biol JI (144):74-500 (1999). Mol Biol JI (144):74-500 (1999).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                               | Heptucyte BKK Signaling Puthway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                                               | 819                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                               | HSVBU91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                               | 4 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| this entropy, fail river happoinna cells that may be used according to these assys are publicly variable (e.g., through the ATCC'N). Exemplany rat liver hapmone dels that may be used according to these assays include Halle cells, which are Known to respond to glucocorticoids, insulta, or cAMP derivatives. |
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|                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                    |

|  |  | "Cardiovascular Disorders" section      |
|--|--|-----------------------------------------|
|  |  | below), dyslinidemia, endocrine         |
|  |  | disorders (as described in the          |
|  |  | "Endocrine Disorders" section           |
|  |  | below), neuropathy, vision              |
|  |  | impairment (e.g., diabetic retinopathy  |
|  |  | and blindness), ulcers and impaired     |
|  |  | wound healing, infection (e.g.,         |
|  |  | infectious diseases and disorders as    |
|  |  | described in the "Infectious            |
|  |  | Diseases" section below, especially     |
|  |  | of the urinary tract and skin), carpal  |
|  |  | tunnel syndrome and Dupuytren's         |
|  |  | contracture). An additional highly      |
|  |  | preferred indication is obesity and/or  |
|  |  | complications associated with           |
|  |  | obesity. Additional highly preferred    |
|  |  | indications include weight loss or      |
|  |  | alternatively, weight gain.             |
|  |  | Additional highly preferred             |
|  |  | indications are complications           |
|  |  | associated with insulin resistance.     |
|  |  | Additional highly preferred             |
|  |  | indications are disorders of the        |
|  |  | musculoskeletal systems including       |
|  |  | myopathies, muscular dystrophy,         |
|  |  | and/or as described herein.             |
|  |  | Additional highly preferred             |
|  |  | indications include, hepatitis,         |
|  |  | jaundice, gallstones, cirrhosis of the  |
|  |  | liver, degenerative or necrotic liver   |
|  |  | disease, alcoholic liver diseases,      |
|  |  | fibrosis, liver regeneration, metabolic |
|  |  | disease, dyslipidemia and               |
|  |  | chlolesterol metabolism.                |
|  |  | Additional highly preferred             |
|  |  | indications include neoplasms and       |

| caneers, girls as legatocarcitonus, other liver ensers, and other and paracentic cancer. Preferred indications also include prostate, breast, ling, esophageal, sommeth, ment, and timing vaneer. Other preferred indications include beinging preferred indications include beinging oppositions include beinging oppositions and pre-trend indications include beinging and example, by specifications, and pre-trend indications and pre-trend indications, and pre-trend indications, and pre-trend indications, and pre-trend indications, and pre-trend indications, and pre-trend indications, and pre-trend indications, and pre-trend indications. | d thighty preferred indexions is a children were than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the another than the |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | insailin are well-known in the art and manilin are well-known well-known in the art and many be used or routinely modified to assess the ability of polyperides of the invention (including authodics and agoniss or entagoniss to the invention) to stimulate insatin secretion. For example, insatin secretion is incusting anti-ort install anti-order and assess and assess and assess that many and also by certain proteins/peptides, and also by certain proteins/peptides, and also by certain proteins/peptides, and discontant proteins/peptides, and discontant proteins/peptides, and discontant proteins/peptides, and discontant proteins/peptides and discontant proteins/peptides and discontant proteins/peptides and also by certain proteins/peptides, and discontant proteins/peptides and agoniss or authorities and annotation of installin secretion (including authodies and agoniss or authorities, 1381-1501-17 (1999), Filinsson, A. A., et al., Am N. X. A., A., A., A., A., M. X. A., A., A., A., A., M. X. A., A., A., M. M. A., A., A., A., A., M. M. X. A., A., A., A., A., M. X. A., A., A., M. M. A., A., A., A., A., A., A., M. X. A., A., A., A., A., A., M. X. A., A., A., A., A., A., M. X. A., A., A., A., A., M. X. A., A., A., A., A., M. X. A., A., A., A., A., A., M. X. A., A., A., A., A., A., M. X. A., A., A., M. X. A., A., A., A., A., A., M. Y. A., A., A., A., A., A., A., A., M. X. A., A., A., A., A., M. Y. A., A., A., A., A., A., M. X. A., A., A., A., A., A., M. Y. A., A., A., A., A., A., A., A., M. Y. A., A., A., A., A., A., A., A., M. Y. A., A., A., A., A., A., A., A., A., A.                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Insulin Secretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 813                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HSVBU91                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 214                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                       | Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-   | "Endocrine Disorders" section<br>below), neuropathy, vision                 |
|-----|---------|-----|-----------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|
|     |         |     |                       | 52 (1996); and, Miraglia S et. al.,                                       | impairment (e.g., diabetic retinopathy                                      |
|     |         |     |                       | Journal of Biomolecular Screening,                                        | and blindness), ulcers and impaired                                         |
|     |         |     |                       | 4:193-204 (1999), the contents of<br>each of which is herein incorporated | wound healing, and infection (e.g.,<br>infectious diseases and disorders as |
|     |         |     |                       | by reference in its entirety.                                             | described in the "Infectious                                                |
|     |         |     |                       | Pancreatic cells that may be used                                         | Diseases" section below, especially                                         |
|     |         |     |                       | according to these assays are publicly                                    | of the urinary tract and skin), carpal                                      |
|     |         |     |                       | available (e.g., through the ATCC120)                                     | 9                                                                           |
|     |         |     |                       | and/or may be routinely generated.                                        | contracture). An additional                                                 |
|     |         |     |                       | Exemplary pancreatic cells that may                                       | highly preferred indication is obesity                                      |
|     |         |     |                       | be used according to mese assays<br>include HTT15 Cells HTT15 are         | and/or complications associated with                                        |
|     |         |     |                       | an adherent epithelial cell line                                          | indications include weight loss or                                          |
|     |         |     |                       | established from Svrian hamster islet                                     | alternatively, weight gain. Additional                                      |
|     |         |     |                       | cells transformed with SV40. These                                        | highly preferred indications are                                            |
|     |         |     |                       | cells express glucagon, somatostatin,                                     | complications associated with insulin                                       |
|     |         |     |                       | and glucocorticoid receptors. The                                         | resistance.                                                                 |
|     |         |     |                       | cells secrete insulin, which is                                           |                                                                             |
|     |         |     |                       | stimulated by glucose and glucagon                                        |                                                                             |
|     |         |     |                       | and suppressed by somatostatin or                                         |                                                                             |
|     |         |     |                       | glucocorticoids. ATTC# CRL-1777                                           |                                                                             |
|     |         |     |                       | Refs: Lord and Ashcroft. Biochem.                                         |                                                                             |
|     |         |     |                       | J. 219: 547-551; Santerre et al. Proc.                                    |                                                                             |
|     |         |     |                       | Natl. Acad. Sci. USA 78; 4339-4343,                                       |                                                                             |
|     |         |     |                       | 1981.                                                                     |                                                                             |
|     | HSVBU91 | 819 | Activation of         | Assays for the activation of                                              | A highly preferred embodiment                                               |
| 214 |         |     | transcription through | transcription through the CD28                                            | of the invention includes a method                                          |
|     |         |     | CD28 response element | response element are well-known in                                        | for stimulating T cell proliferation.                                       |
|     |         |     | in immune cells (such | the art and may be used or routinely                                      | An alternative highly preferred                                             |
|     |         |     | as T-cells).          | modified to assess the ability of                                         | embodiment of the invention                                                 |
|     |         |     |                       | polypeptides of the invention                                             | 44                                                                          |
|     |         |     |                       | (including antibodies and agonists or                                     | cell proliferation. A highly                                                |
|     |         |     |                       | antagonists of the invention) to                                          | preferred embodiment of the                                                 |
|     |         |     |                       | stimulate IL-2 expression in T cells.                                     | invention includes a method for                                             |
|     |         |     |                       | Exemplary assays for transcription                                        | activating T cells. An alternative                                          |

| highly preferred embodiment of the | invention includes a method for |                                | inactivating T cells. A highly      | preferred embodiment of the         | invention includes a method for    | stimulating (e.g., increasing) IL-2    | production. An alternative highly   | preferred embodiment of the | invention includes a method for | inhibiting (e.g., reducing) IL-2    | production. Additional highly    | preferred indications include | inflammation and inflammatory     | disorders. Highly preferred     | indications include autoimmune      | diseases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,        | multiple sclerosis and/or as described | below), immunodeficiencies (e.g., as | described below), boosting a T cell-   | mediated immune response, and | suppressing a T cell-mediated                 | immune response. An additional      | highly preferred indication includes | infection (e.g., AIDS, and/or as | elor                             | Disease"). Highly preferred | indications include neoplastic | diseases (e.g., melanoma, renal cell | carcinoma, leukemia, lymphoma, | and/or as described below under | "Hyperproliferative Disorders"). | Highly preferred indications include | neoplasms and cancers, such as, for | example, melanoma (e.g., metastatic |
|------------------------------------|---------------------------------|--------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-----------------------------|---------------------------------|-------------------------------------|----------------------------------|-------------------------------|-----------------------------------|---------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|-------------------------------|-----------------------------------------------|-------------------------------------|--------------------------------------|----------------------------------|----------------------------------|-----------------------------|--------------------------------|--------------------------------------|--------------------------------|---------------------------------|----------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|
| through the CD28 response element  | that may be used or routinely   | modified to test CD28-response | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in | Enzymol 216:362-368 (1992);     | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); McGuire | and Iacobelli, J Immunol      | 159(3):1319-1327 (1997); Parra et | al., J Immunol 166(4):2437-2443 | (2001); and Butscher et al., J Biol | Chem 3(1):552-560 (1998), the         | contents of each of which are herein | incorporated by reference in its       | entirety. T cells that may be used   | according to these assays are publicly | available (e.g., through the  | ATCC <sup>TM</sup> ). Exemplary human T cells | that may be used according to these | assays include the JURKAT cell line, | which is a suspension culture of | leukemia cells that produce IL-2 | when stimulated.            |                                |                                      |                                |                                 |                                  |                                      |                                     |                                     |
|                                    |                                 |                                |                                     |                                     |                                    |                                        |                                     |                             |                                 |                                     |                                  |                               |                                   |                                 |                                     |                                       |                                      |                                        |                                      |                                        |                               |                                               |                                     |                                      |                                  |                                  |                             |                                |                                      |                                |                                 |                                  |                                      |                                     |                                     |
|                                    |                                 |                                |                                     |                                     |                                    |                                        |                                     |                             |                                 |                                     |                                  |                               |                                   |                                 |                                     |                                       |                                      |                                        |                                      |                                        |                               |                                               |                                     |                                      |                                  |                                  |                             |                                |                                      |                                |                                 |                                  |                                      |                                     |                                     |
|                                    |                                 |                                |                                     |                                     |                                    |                                        |                                     |                             |                                 |                                     |                                  |                               |                                   |                                 |                                     |                                       |                                      |                                        |                                      |                                        |                               |                                               |                                     |                                      |                                  |                                  |                             |                                |                                      |                                |                                 |                                  |                                      |                                     |                                     |

| (e.g., metastane renal cen | (e.g., T cell lymphoma), and prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver and | urinary cancer. Other preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. A highly | preferred indication is infection (e.g., | tuberculosis, infections associated | with granulomatous disease, and | osteoporosis, and/or an infectious | disease as described below under | "Infectious Disease"). A highly | preferred indication is AIDS. | Additional highly preferred | indications include suppression of | immune reactions to transplanted | organs and/or tissues, uveitis, | psoriasis, and tropical spastic | paraparesis. Preferred indications | include blood disorders (e.g., as | described below under "Immune | Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications | also include anemia, pancytopenia, | leukopenia, thrombocytopenia, | Hodgkin's disease, acute | lymphocytic anemia (ALL), | plasmacytomas, multiple myeloma, | Burkitt's lymphoma, arthritis, |  |
|----------------------------|----------------------------------------|----------------------------------|---------------------------------------|---------------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------------------------------|----------------------------|------------------------------------------|-------------------------------------|---------------------------------|------------------------------------|----------------------------------|---------------------------------|-------------------------------|-----------------------------|------------------------------------|----------------------------------|---------------------------------|---------------------------------|------------------------------------|-----------------------------------|-------------------------------|---------------------------|------------------------------------|------------------------------------|------------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------------|--------------------------------|--|
|                            |                                        |                                  |                                       |                                 |                            |                                     |                                     |                                   |                            |                                          |                                     |                                 |                                    |                                  |                                 |                               |                             |                                    |                                  |                                 |                                 |                                    |                                   |                               |                           |                                    |                                    |                                    |                               |                          |                           |                                  |                                |  |

| neurophilia, hemophilia,<br>hypercoagulation, diabetes mellitus,<br>endocarditis, meningitis, Lyme<br>Disease, astima and allergy. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|                                                                                                                                    | Assays for the activation of the AMP assays for the activation of the response cleaned are well-known in the ent and may be used or outning the medical to assess the ability of polytopities of the invention) to increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increase chalf, regulate CRB1 increased to deed to incurb in outnative the chalf in activate the chalf in activate the chalf in activate the chalf in adhogenesis, and is involved in all adhogenesis, and is involved in adhogenesis, and is involved in adhogenesis, and is involved in adhogenesis, and is involved in adhogenesis, and is the containing and incurrent that may be used or numirately medified to test chalf in reasonise element that may be used or incutating medical to the invention including analysis, Cullen and Mann. Methods in Ingest et al. 18, 1852-284, 1953, L Include assays desioned in Berger et al. 18, 1852-284, 1954, L Include and Mann. Methods in Ingest et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1954, L Include et al. 18, 1852-284, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 1854, 18 |
|                                                                                                                                    | Activation to the control of transcription through transcription through expense cleaned (AE) in pre- adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocytes, adjocyte |
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|                                                                                                                                    | HSXGl47                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                    | 215                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| T.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| impairment (e.g., diabetic retinopathy are ab findess), those and impaired wound beding, and infection (e.g., arefection season and disorders as described in the "Infections Bassess" section below, especially of the unimary tract and skin), carpal turned syndroms and Dapayten's courseture). Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 6346 (1988); Rensach et al., Mol Cell Pap (20) (2000); and Klemm et al., 180 (Chen 273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273:917-273 | assas for the regulation (i.e., increases or decreases) of virability and proliferation of cells in vitro are well-known in the at and may be used or rountedly modified to assess the ability of polypropides of the invention (including antihodies and grayests or attentions) or regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Giob Luminescent Cell lines is ree recomple, the CellTiter-Giob Luminescent Cell Madison, WI, USA) can be used to Madison, WI, USA) can be used to measure the numero of viable cells in celline placed on quantification of the cells. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | infiliration of pre-<br>adipose cells (such as<br>373-L1 cells)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 619                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Progressor which signals the progressor of metabolically active cells. 3174-11 is a monor entracheory cell mine. It is a continuous substant of 318 and of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the cells of the ce | cxumple an GSK-3 kinnes assay, for cxumple an GSK-3 kinnes assay, from the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the analysis of the ana |
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| alternative highly preferred embodiment of the invention includes a method for inhibiting mustle cell differentiation. In a mostle, on the differentiation, in a mostle cell formwall and the mostle.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | seption embodiems, seed at musce cell differentiation is infinited. Highly preferred indications include disorders of the musculoskeleal system. Preferred indications include tropolisis diseases (e.g. as described below under responsable below under septions are bisorders), superpondification bisorders. | described below under "Tradocrine described below under "Tradocrine described below under "Neun (e.g., as described below under "Neun (e.g., as described below under "Neun (e.g., as described below under "Immune described delow under "Immune described delow under "Immune described delow under "Immune "Autry", "Cardonivascular and or" "Blood-Related Disorders", and or "Blood-Related Disorders", and or "Blood-Related | blooker's) imment desorders (e.g., as described below under "Immune desorders) immune desorders (e.g., as described below under "Infections (e.g., as described below under "Infections (e.g., as described below under "Infections (e.g., as deserted indection is diabetes mellitus, An audditional lighly preferred indection is delabores mellitus, and audditional lighly preferred indection is semiplication. | daroctive transpants, tanstern<br>rephropathy, kidney disease (e.g.,<br>renal failure, nephropathy and/or<br>other diseases and disorders as<br>described in the Yenal Disorders'<br>section below), diabetic neuropathy,<br>nerve disease and nerve demange (e.g. |
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| of each of which are herein incorporated by reference in its entirely. Rat myoblast cells that may be used according to these assays are matical control of the each the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the co | ATOMOTO STATE THE THE THE THE THE THE THE THE THE T                                                                                                                                                                                                                                                              | media.                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                    |
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|  | due to diabetic neumonathy) blood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|  | vessel blockage, near disease,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | stroke, impotence (e.g., due to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | diabetic neuropathy or blood vessel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | blockage), seizures, mental                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | confusion, drowsiness, nonketotic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | hyperglycemic-hyperosmolar coma,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | cardiovascular disease (e.g., heart                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | disease, atherosclerosis,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|  | microvascular disease, hypertension,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | stroke, and other diseases and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | disorders as described in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | "Cardiovascular Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | below), dyslipidemia, endocrine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | disorders (as described in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | "Endocrine Disorders" section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | below), neuropathy, vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | impairment (e.g., diabetic retinopathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | and blindness), ulcers and impaired                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | wound healing, infections (e.g.,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | infectious diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | described in the "Infectious                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | Diseases" section below, especially                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | of the urinary tract and skin), carpal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | tunnel syndrome and Dupuytren's                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | contracture). An additional                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | highly preferred indication is obesity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | and/or complications associated with                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | obesity. Additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | indications include weight loss or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | alternatively, weight gain.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | Additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | indications are complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | Additional highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | indications are disorders of the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | musculoskeletal system including                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| myopalities, muscular dystrophy, and ora a described herein, Additional lighty preferred infactions include; myopathy, archity, congestive heart failure, exceptive, congestive heart failure, exceptive, myopathy, archity, congestive heart failure, exceptive, congestive heart failure, exceptive, myopathy, archity, congestive heart failure, exceptive, myopathy, exceptive disciplinations include exceptive disciplinations include exceptive disciplinations include exceptive preferred indications include prepared include the preferred indications include prepared include the preferred indications include prepared include the preferred indications include prepared include disciplinations, and its prepared include disciplinations, and its prepared include includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared includes and its prepared inc | Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activation of Activ |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSYAZ63                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| acti    | activity of polypeptides of the        | invention includes a method for        |
|---------|----------------------------------------|----------------------------------------|
| inve    | invention (including antibodies and    | stimulating adipocyte differentiation. |
| agoi    | agonists or antagonists of the         | An alternative highly preferred        |
| inve    | invention) include assays disclosed in | embodiment of the invention            |
| Fon     | Forrer et al., Biol Chem 379(8-        | includes a method for inhibiting       |
| 1:(6    | 9):1101-1110 (1998); Nikoulina et      | adipocyte differentiation. Highly      |
| al.,]   | al., Diabetes 49(2):263-271 (2000);    | preterred indications include          |
| and     | and Schreyer et al., Diabetes          | endocrine disorders (e.g., as          |
| 48(8    | 48(8):1662-1666 (1999), the contents   | described below under "Endocrine       |
| ofe     | of each of which are herein            | Disorders"). Preferred indications     |
| inco    | incorporated by reference in its       | include neoplastic diseases (e.g.,     |
| entii   | entirety. Mouse adipocyte cells that   | lipomas, liposarcomas, and/or as       |
| may     | may be used according to these         | described below under                  |
| assa    | assays are publicly available (e.g.,   | "Hyperproliferative Disorders"),       |
| thro    | through the ATCCTM). Exemplary         | blood disorders (e.g., hypertension,   |
| nou     | mouse adipocyte cells that may be      | congestive heart failure, blood vessel |
| osn     | used according to these assays         | blockage, heart disease, stroke,       |
| incl    | include 3T3-L1 cells. 3T3-L1 is an     | impotence and/or as described below    |
| adh     | adherent mouse preadipocyte cell       | under "Immune Activity",               |
| line    | ine that is a continous substrain of   | "Cardiovascular Disorders", and/or     |
| 3T3     | 3T3 fibroblast cells developed         | "Blood-Related Disorders"), immune     |
| orth    | through clonal isolation and undergo   | disorders (e.g., as described below    |
| apn     | a pre-adipocyte to adipose-like        | under "Immune Activity"), neural       |
| con     | conversion under appropriate           | disorders (e.g., as described below    |
| diffi   | differentiation conditions known in    | under "Neural Activity and             |
| the art | art.                                   | Neurological Diseases"), and           |
|         |                                        | infection (e.g., as described below    |
|         |                                        | under "Infectious Disease"). A         |
|         |                                        | highly preferred indication is         |
|         |                                        | diabetes mellitus. An                  |
|         |                                        | additional highly preferred indication |
|         |                                        | is a complication associated with      |
|         |                                        | diabetes (e.g., diabetic retinopathy,  |
|         |                                        | diabetic nephropathy, kidney disease   |
|         |                                        | (e.g., renal failure, nephropathy      |
|         |                                        | and/or other diseases and disorders as |
|         |                                        | described in the "Renal Disorders"     |

|  |     | section helow) diabetic neuronathy       |
|--|-----|------------------------------------------|
|  |     | course discount and mount demonstration, |
|  |     | nerve disease and nerve damage (e.g.,    |
|  |     | due to diabetic neuropathy), blood       |
|  | _   | vessel blockage, heart disease,          |
|  | 8   | stroke, impotence (e.g., due to          |
|  |     | diabetic neuropathy or blood vessel      |
|  |     | blockage), seizures, mental              |
|  |     | confusion, drowsiness, nonketotic        |
|  | 1   | hyperglycemic-hyperosmolar coma,         |
|  | -   | cardiovascular disease (e.g., heart      |
|  | -   | disease, atherosclerosis,                |
|  |     | microvascular disease, hypertension,     |
|  | -   | stroke, and other diseases and           |
|  | -0  | disorders as described in the            |
|  | -   | "Cardiovascular Disorders" section       |
|  |     | below), dyslipidemia, endocrine          |
|  |     | disorders (as described in the           |
|  | •   | "Endocrine Disorders" section            |
|  |     | below), neuropathy, vision               |
|  | ī   | impairment (e.g., diabetic retinopathy   |
|  | -   | and blindness), ulcers and impaired      |
|  | _   | wound healing, infection (e.g.,          |
|  |     | infectious diseases and disorders as     |
|  | -5  | described in the "Infectious             |
|  | I   | Diseases" section below, especially      |
|  |     | of the urinary tract and skin), carpal   |
|  | -   | me                                       |
|  | -   | contracture). An additional              |
|  |     | highly preferred indication is obesity   |
|  | 100 | and/or complications associated with     |
|  |     | obesity. Additional highly preferred     |
|  |     | indications include weight loss or       |
|  | -   | alternatively, weight gain.              |
|  | 7   | Additional highly preferred              |
|  | i   | indications are complications            |
|  | 8   | associated with insulin resistance.      |
|  | /   | Additional highly preferred              |

|     |         |     |                       |                                       | indications are disorders of the        |
|-----|---------|-----|-----------------------|---------------------------------------|-----------------------------------------|
|     |         |     |                       |                                       | musculoskeletal systems including       |
|     |         |     |                       |                                       | myopathies, muscular dystrophy,         |
|     |         |     |                       |                                       | and/or as described herein.             |
|     |         |     |                       |                                       | Additional highly preferred             |
|     |         |     |                       |                                       | indications include, hypertension,      |
|     |         |     |                       |                                       | coronary artery disease,                |
|     |         |     |                       |                                       | dyslipidemia, gallstones,               |
|     |         |     |                       |                                       | osteoarthritis, degenerative arthritis, |
|     |         |     |                       |                                       | eating disorders, fibrosis, cachexia,   |
|     |         |     |                       |                                       | and kidney diseases or disorders.       |
|     |         |     |                       |                                       | Highly preferred indications include    |
|     |         |     |                       |                                       | neoplasms and cancer, such as,          |
|     |         |     |                       |                                       | lipoma, liposarcoma, lymphoma,          |
|     |         |     |                       |                                       | leukemia and breast, colon, and         |
|     |         |     |                       |                                       | kidney cancer. Additional highly        |
|     |         |     |                       |                                       | preferred indications include           |
|     |         |     |                       |                                       | melanoma, prostate, lung,               |
|     |         |     |                       |                                       | pancreatic, esophageal, stomach,        |
|     |         |     |                       |                                       | brain, liver, and urinary cancer.       |
|     |         |     |                       |                                       | Other preferred indications include     |
|     |         |     |                       |                                       | benign dysproliferative disorders and   |
|     |         |     |                       |                                       | pre-neoplastic conditions, such as,     |
|     |         |     |                       |                                       | for example, hyperplasia, metaplasia,   |
|     |         |     |                       |                                       | and/or dysplasia.                       |
|     | HSYAZ63 | 620 | Activation of         | Assays for the activation of          | Highly preferred indications include    |
| 216 |         |     | transcription through | transcription through the Gamma       | neoplastic diseases (e.g., leukemia,    |
|     |         |     | GAS response element  | Interferon Activation Site (GAS)      | lymphoma, and/or as described           |
|     |         |     | in immune cells (such | response element are well-known in    | below under "Hyperproliferative         |
|     |         |     | as T-cells).          | the art and may be used or routinely  | Disorders"). Highly preferred           |
|     |         |     |                       | modified to assess the ability of     | indications include neoplasms and       |
|     |         |     |                       | polypeptides of the invention         | cancers, such as, for example,          |
|     |         |     |                       | (including antibodies and agonists or | leukemia, lymphoma (e.g., T cell        |
|     |         |     |                       | antagonists of the invention) to      | lymphoma, Burkitt's lymphoma,           |
|     |         |     |                       | regulate STAT transcription factors   | non-Hodgkins lymphoma, Hodgkin"s        |
|     |         |     |                       | and modulate gene expression          | disease), melanoma, and prostate,       |
|     |         |     |                       | involved in a wide variety of cell    | breast, lung, colon, pancreatic,        |

| functions. Exemplary assays for       | esophageal, stomach, brain, liver and   |
|---------------------------------------|-----------------------------------------|
| transcription through the GAS         | urinary cancer. Other preferred         |
| response element that may be used or  | indications include benign              |
| routinely modified to test GAS-       | dysproliferative disorders and pre-     |
| response element activity of          | neoplastic conditions, such as, for     |
| polypeptides of the invention         | example, hyperplasia, metaplasia,       |
| (including antibodies and agonists or | and/or dysplasia. Preferred             |
| antagonists of the invention) include | indications include autoimmune          |
| assays disclosed in Berger et al.,    | diseases (e.g., rheumatoid arthritis,   |
| Gene 66:1-10 (1998); Cullen and       | systemic lupus erythematosis,           |
| Malm, Methods in Enzymol              | multiple sclerosis and/or as described  |
| 216:362-368 (1992); Henthorn et al.,  | below), immunodeficiencies (e.g., as    |
| Proc Natl Acad Sci USA 85:6342-       | described below), boosting a T cell-    |
| 6346 (1988); Matikainen et al.,       | mediated immune response, and           |
| Blood 93(6):1980-1991 (1999); and     | suppressing a T cell-mediated           |
| Henttinen et al., J Immunol           | immune response. Additional             |
| 155(10):4582-4587 (1995), the         | preferred indications include           |
| contents of each of which are herein  | inflammation and inflammatory           |
| incorporated by reference in its      | disorders. Highly preferred             |
| entirety. Exemplary human T cells,    | indications include blood disorders     |
| such as the SUPT cell line, that may  | (e.g., as described below under         |
| be used according to these assays are | "Immune Activity", "Blood-Related       |
| publicly available (e.g., through the | Disorders", and/or "Cardiovascular      |
| ATCCTM).                              | Disorders"), and infection (e.g., viral |
|                                       | infections, tuberculosis, infections    |
|                                       | associated with chronic                 |
|                                       | granulomatosus disease and              |
|                                       | malignant osteoporosis, and/or an       |
|                                       | infectious disease as described below   |
|                                       | under "Infectious Disease"). An         |
|                                       | additional preferred indication is      |
|                                       | idiopathic pulmonary fibrosis.          |
|                                       | Preferred indications include anemia,   |
|                                       | pancytopenia, leukopenia,               |
|                                       | thrombocytopenia, acute                 |
|                                       | lymphocytic anemia (ALL),               |
|                                       | plasmacytomas, multiple myeloma,        |

| 217 | HSYBG37 | 621 | Activation of Adipocyte ERK | Kinase assay, Kinase assays, for<br>example an Elk-I kinase assays, for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | disease, inflammatory bowe disease, seeks, neuropastors, seeks, neuropaila, seeks, neuropaila, sporiais, supression of immune reactions to ramplanted organs and tracks, hemophical, supressignation, disease, hemophical, supressignation, disease, seeks, hemophical, for hyperosquitation, disease, and safimm and altergy.  Disease, and safimm and altergy.  A flight ported embodiment of the invention includes a method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----|---------|-----|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |         |     | Signaling Pathway           | FIRK Signal transic assist, not present a proper at remember of differentiation are well known in the art and may be upon for proper of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the c | to a time mention misses a meanor for simulating adipocyte profession, an administration, and information preferred embediment of the mention includes as method for inhibiting adipocyte proliferation. A suffix preferred embediment of the timention includes a method for inhibiting adipocyte differentiation. An admensive highly preferred embediment of the invention includes a method for mithing adipocyte differentiation. An admensive highly preferred administration of the invention includes as method for mithing adipocyte differentiation. A mithing preferred method for mithing adipocyte differentiation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|     |         |     |                             | and challed and the challed and goods and agoins or an anagonists of the invention include as ways disclosed in Forrer et al., Biod Chem 379(4-5);1101-1110 (1995), Le Marchand-Brusder Y. Exp (Chem 1799), Le Marchand-Brusder Y. Exp (1995), Le Challed Chem 1799, Lycrakis JM, Challed Chem 1799, Lycrakis JM, Chang and Karin Nature 4104(6524);57-40 (2001); and Cobb 1411, For Biothys, Mod Biod 71(4-4)-49/49-500 (1999); the contents of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | adjocyte activation. An alternative adjocyte activation. An alternative inhebit preferred embodiment of the invention includes a method for inhibiting the activation of Co.g. inhibiting the activation of Co.g. inhibiting the activation of Co.g. inhibiting the activation of Co.g. inhibiting the activation of Co.g. inhibiting the activation of Co.g. in inhibiting the activation of activation and adjocytes. Highly preferred indications inhibiting the activation below under "Endocrine Disorders"). Highly preferred indications also linging preferred indications also include neoplastic diseases (e.g., an include neoplastic diseases (e.g., an include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., and include neoplastic diseases (e.g., an |

| incorporated by reference in is incorporated by reference in is entirety. Mouse adapoyer cells that may be used according to these assays are publicly available (e.g., through the ATCCPs). Esemplary mouse adjacyor cells that may be used according to these assays include 371-Li is an adherent mouse preadpoyer cell but may be used according to these assays and public that that is a continuous substrain of 3173 fibrohists cells developed through donal isolation and undergo a pre-adipoyer of adaposed its conversation made appropriate differentiation conditions known in the art. |
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|  | discontinuo opposito                    |
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|  | contraction discons frameworks          |
|  | microvascinar disease, hypercension,    |
|  | SHOKE, and other diseases and           |
|  | disorders as described in the           |
|  | "Cardiovascular Disorders" section      |
|  | below), dyslipidemia, endocrine         |
|  | disorders (as described in the          |
|  | "Endocrine Disorders" section           |
|  | below), neuropathy, vision              |
|  | impairment (e.g., diabetic retinopathy  |
|  | and blindness), ulcers and impaired     |
|  | wound healing, infection (e.g.,         |
|  | infectious diseases and disorders as    |
|  | described in the "Infectious            |
|  | Diseases" section below (particularly   |
|  | of the urinary tract and skin). An      |
|  | additional highly preferred indication  |
|  | is obesity and/or complications         |
|  | associated with obesity. Additional     |
|  | highly preferred indications include    |
|  | weight loss or alternatively, weight    |
|  | gain. Additional highly                 |
|  | preferred indications are               |
|  | complications associated with insulin   |
|  | resistance. Additional highly           |
|  | preferred indications are disorders of  |
|  | the musculoskeletal systems             |
|  | including myopathies, muscular          |
|  | dystrophy, and/or as described          |
|  | herein. Additional highly               |
|  | preferred indications include,          |
|  | hypertension, coronary artery           |
|  | disease, dyslipidemia, gallstones,      |
|  | osteoarthritis, degenerative arthritis, |
|  | eating disorders, fibrosis, cachexia,   |
|  | and kidney diseases or disorders.       |
|  | Preferred indications include           |

|     |         |     |                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | lymphoma, Italicania and breast, Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson and Johnson a |
|-----|---------|-----|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 217 | HSYBG37 | 621 | Activation of DIX  Activation of DIX  signature cols (souch as evainophils). | Kinnes assay. JNK kinnes assays for<br>gazalt transchorton that regular cell<br>proliferation, activation, or appropriate<br>gazalt transchorton, activation, or appropriate<br>to well known in the art and may be<br>used or routinely modified to assess<br>used or routinely modified to assess<br>the ability of poppsychies of the<br>invention (including antibodics and<br>gazonists or magionists of the<br>invention) to promote or inhinit cell<br>invention) to promote or inhinit cell<br>invention) to promote or inhinit cell<br>appropriate, Reemplary assays for<br>appropriate, Reemplary assays for<br>appropriates of the invention<br>or routinely modified to test JNK<br>Keniase activity of an mybe used<br>or routinely modified to test JNK<br>Keniase activity and mybe used<br>polypeptides of the invention include<br>antiboding ambidous and agentists or<br>antagonists of the invention include<br>polypeptides of the invention include<br>antagonists of the invention include<br>antagonists of the invention include<br>124702; 405-504 (1999); Krinkis a<br>24702; 405-504 (1999); Krinkis is<br>Almortan Sexam fed.248. | Highly preferred indications include and any angular preparation, and any angular propersistivity reactions, inflammatory deaders. Additional highly preferred indications include ingular preferred indications include in the present present present and any and support of the present present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present of the present  |

| eosinophil-mediated immune       | response, and suppressing an<br>cosinophil-mediated immune | response.                |                                  |                                    |                                   |                                      |                                         |                                          |                              |                                 |                               |                                      |                                   |                               |                                       |                                  |                                    |                                         |                               |                                      |                              |                                 |                                      |                                  |                                      |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          |
|----------------------------------|------------------------------------------------------------|--------------------------|----------------------------------|------------------------------------|-----------------------------------|--------------------------------------|-----------------------------------------|------------------------------------------|------------------------------|---------------------------------|-------------------------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|----------------------------------|------------------------------------|-----------------------------------------|-------------------------------|--------------------------------------|------------------------------|---------------------------------|--------------------------------------|----------------------------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------|------------------------------------|------------------------------------|----------------------------------------|--------------------------|
| 410(6824);37-40 (2001); and Cobb | 4):479-500 (1999); the contents of                         | each of which are herein | incorporated by reference in its | entirety. Exemplary cells that may | be used according to these assays | include cosinophils. Eosinophils are | important in the late stage of allergic | reactions; they are recruited to tissues | and mediate the inflammatory | response of late stage allergic | reaction. Moreover, exemplary | assays that may be used or routinely | modified to assess the ability of | polypeptides of the invention | (including antibodics and agonists or | antagonists of the invention) to | modulate signal transduction, cell | proliferation, activation, or apoptosis | in cosinophils include assays | disclosed and/or cited in: Zhang JP, | et al., "Role of caspases in | dexamethasone-induced apoptosis | and activation of c-Jun NH2-terminal | kinase and p38 mitogen-activated | protein kinase in human cosinophils" | Clin Exp Immunol; Oct;122(1):20-7 | (2000); Hebestreit H, et al., | "Disruption of fas receptor signaling | by nitric oxide in eosinophils" J Exp | Med; Feb 2;187(3):415-25 (1998); J | Allergy Clin Immunol 1999 | Sep;104(3 Pt 1):565-74; and, Sousa | AR, et al., "In vivo resistance to | corticosteroids in bronchial asthma is | associated with enhanced |
|                                  |                                                            | _                        |                                  |                                    |                                   |                                      |                                         |                                          |                              |                                 |                               |                                      |                                   |                               |                                       |                                  |                                    |                                         |                               |                                      |                              |                                 |                                      |                                  |                                      |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          |
|                                  |                                                            |                          |                                  |                                    |                                   |                                      |                                         |                                          |                              |                                 |                               |                                      |                                   |                               |                                       |                                  |                                    |                                         |                               |                                      |                              |                                 |                                      |                                  |                                      |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        | _                        |

| assays are publicly available (e.g., through the ATCC <sup>TM</sup> ). Exemplary | "Hyperproliferative Disorders"),<br>blood disorders (e.g., as described |
|----------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| rat liver hepatoma cells that may be used according to these assays              | below under "Immune Activity",<br>"Cardiovascular Disorders", and/or    |
| include H4lle cells, which are known                                             |                                                                         |
| to respond to glucocorticoids, insulin,                                          | disorders (e.g., as described below                                     |
|                                                                                  | disorders (e.g., as described below                                     |
|                                                                                  | under "Neural Activity and                                              |
|                                                                                  | Neurological Diseases"), and                                            |
|                                                                                  | infection (e.g., as described below                                     |
|                                                                                  | under "Infectious Disease").                                            |
|                                                                                  | Ę.                                                                      |
|                                                                                  | diabetes mellitus. An additional                                        |
|                                                                                  | highly preferred indication is a                                        |
|                                                                                  | complication associated with                                            |
|                                                                                  | diabetic nenhannathy kidney disease                                     |
|                                                                                  | (e.g., renal failure, nephropathy                                       |
|                                                                                  | and/or other diseases and disorders as                                  |
|                                                                                  | described in the "Renal Disorders"                                      |
|                                                                                  | section below), diabetic neuropathy,                                    |
|                                                                                  | nerve disease and nerve damage                                          |
|                                                                                  | (e.g., due to diabetic neuropathy),                                     |
|                                                                                  | stroke, impotence (e.g., due to                                         |
|                                                                                  | diabetic neuropathy or blood vessel                                     |
|                                                                                  | blockage), seizures, mental                                             |
|                                                                                  | confusion, drowsiness, nonketotic                                       |
|                                                                                  | hyperglycemic-hyperosmolar coma,                                        |
|                                                                                  | cardiovascular disease (e.g., heart                                     |
|                                                                                  | disease, atherosclerosis,                                               |
|                                                                                  | microvascular disease, hypertension,                                    |
|                                                                                  | stroke, and other diseases and                                          |
|                                                                                  | disorders as described in the                                           |
|                                                                                  | "Cardiovascular Disorders" section                                      |
|                                                                                  | below), dyslipidemia, endocrine                                         |

|   | ,        |                                         |
|---|----------|-----------------------------------------|
|   | -        |                                         |
|   |          | "Endocrine Disorders" section           |
|   | 4        | below), neuropathy, vision              |
|   | -12      | impairment (e.g., diabetic retinopathy  |
|   | B        | and blindness), ulcers and impaired     |
|   | 8        | wound healing, infection (e.g.,         |
|   | ii       | infectious diseases and disorders as    |
|   | P        | described in the "Infectious            |
|   | 1        | Diseases" section below, especially     |
|   | •        | of the urinary tract and skin), carpal  |
|   | t t      | tunnel syndrome and Dupuytren's         |
|   | 0        | contracture). An additional highly      |
|   | <u>a</u> | preferred indication is obesity and/or  |
|   | 9        | complications associated with           |
|   | 0        | obesity. Additional highly preferred    |
|   |          | indications include weight loss or      |
|   | 8        | alternatively, weight gain.             |
|   | ~        | Additional highly preferred             |
|   |          | indications are complications           |
|   | B        | associated with insulin resistance.     |
|   | 4        | Additional highly preferred             |
|   |          | indications are disorders of the        |
|   | <u> </u> | musculoskeletal systems including       |
|   | п        | myopathies, muscular dystrophy,         |
| _ | B        | and/or as described herein.             |
|   | •        | Additional highly preferred             |
|   |          | indications include, hepatitis,         |
|   | <u> </u> | jaundice, gallstones, cirrhosis of the  |
|   | -        | liver, degenerative or necrotic liver   |
|   | P        | disease, alcoholic liver diseases,      |
|   | g        | fibrosis, liver regeneration, metabolic |
|   | P        | disease, dyslipidemia and               |
|   | 0        | chlolesterol metabolism.                |
|   | <u> </u> | Additional highly preferred             |
|   |          | indications include neoplasms and       |
|   | 0        | cancers, such as, hepatocarcinomas,     |
|   | 0        | other liver cancers, and colon and      |

| pancratic conter, Preferred indications also include prostate, herest, lung, expolated, stormerl, benia, and utmory cancer. Other preferred indications include benign dysponitientient claisteders and pre- incophastic conditions, such as, for example, poptibists, metaphists, and/or dysplistin. | Caspace Assays A rhighly prefered ambediment of for expose apoptosis rescue are well the invention includes a method for caspace apoptosis rescue are well and the invention includes a method for mishing aposits of the polypeptides of the moderate to the invention furbuling ambedies and protessentediated apoptosis. Seemplots of the invention includes a method for mishing protessentediated apoptosis. Seemplot in the invention of the invention includes a method for mishing protessentediated apoptosis are stead or proposition of the invention includes a method for mishing apoptosis rescue of polyperides of the invention includes a method for mishing and agonists or antagonists of the invention includes a method for including and the invention includes a method for including and adjusting and apoptosis seems of polyperides of inhibiting endothelial cell provide the invention includes a method for including and the invention includes a method for similaring feed (1999); and A Atheroesider inhibiting includes a method for infinite including and for infinite endothelial cell growth. A highly preferred embodiment of the invention included which for similaring endothelial cell growth. A highly preferred embodiment of the invention included which for similaring endothelial cell growth. A highly preferred embodiment of the invention included which for similaring endothelial cell growth. A highly preferred embodiment of the invention included which for similaring endothelial cell growth. A highly preferred embodiment of the invention includes a method for invention includes an embodiment of the invention includes an embodiment of the invention includes an embodiment of the invention includes an embod for a method or intention included in a proper seed of the invention in |
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|                                                                                                                                                                                                                                                                                                       | Protection from  Caspaes Apoptosis Researe. Assa  Apoptosis.  Apoptosis.  Apoptosis.  Included in the art and may be used  routinely modified to assess the ability of the polyperplaties of the aposts or antigomists of the pubperplaties of the aposts or antigomists of the apoptosis.  Exemplary assays for engages protected in thirth caspaes protected in thirth caspaes protected in the apoptosis or antigomists of the aposts or antigomists of the caspaes protected in the apoptosis or antigomists of the apoptosis that may be used or antinely modified to test caspaes apoptosis is a continely modified to test caspaes apoptosis season of polyperplates and agonisis reacted of polyperplates and agonisis or antigomists of the invention) include the assays alteration) include the assays alteration of the contents of each of which are beer in the contents of each of which are beer in contents of each of which are beer per producted or antigomist of the contents of each of which are beer the trace of the protection of the contents of the trace of the seasons publicly available (e.g., through connected as ources). Exemplary connected as ources). Exemplary connected as ources). Exemplary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                       | HTABE28 623                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                       | 219                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| of the vessels themselves, such as of | the arteries, capillaries, veins and/or | lymphatics). Highly preferred are | indications that stimulate | angiogenesis and/or | cardiovascularization. Highly | preferred are indications that inhibit | angiogenesis and/or | cardiovascularization. Highly | preferred indications include | antiangiogenic activity to treat solid | tumors, leukemias, and Kaposi"s | sarcoma, and retinal disorders. | Highly preferred indications include | neoplasms and cancer, such as, | Kaposi"s sarcoma, hemangioma | (capillary and cavernous), glomus | tumors, telangiectasia, bacillary | angiomatosis, | hemangioendothelioma, | angiosarcoma, | haemangiopericytoma, | lymphangioma, lymphangiosarcoma. | Highly preferred indications also | include cancers such as, prostate, | breast, lung, colon, pancreatic, | esophageal, stomach, brain, liver, | and urinary cancer. Preferred | indications include benign | dysproliferative disorders and pre- | neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Highly | preferred indications also include | arterial disease, such as, | atherosclerosis, hypertension, |
|---------------------------------------|-----------------------------------------|-----------------------------------|----------------------------|---------------------|-------------------------------|----------------------------------------|---------------------|-------------------------------|-------------------------------|----------------------------------------|---------------------------------|---------------------------------|--------------------------------------|--------------------------------|------------------------------|-----------------------------------|-----------------------------------|---------------|-----------------------|---------------|----------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|------------------------------------|-------------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------------------------------|--------------------------|------------------------------------|----------------------------|--------------------------------|
|                                       |                                         |                                   |                            |                     |                               |                                        |                     |                               |                               |                                        |                                 |                                 |                                      |                                |                              |                                   |                                   |               |                       |               |                      |                                  |                                   |                                    |                                  |                                    |                               |                            |                                     |                                     |                                   |                          |                                    |                            |                                |
|                                       |                                         |                                   |                            |                     |                               |                                        |                     |                               |                               |                                        |                                 |                                 |                                      |                                |                              |                                   |                                   |               |                       |               |                      |                                  |                                   |                                    |                                  |                                    |                               |                            |                                     |                                     |                                   |                          |                                    |                            |                                |
| _                                     |                                         |                                   |                            |                     |                               |                                        |                     |                               |                               |                                        |                                 |                                 |                                      |                                |                              |                                   |                                   |               |                       |               |                      |                                  |                                   |                                    |                                  |                                    |                               |                            |                                     |                                     |                                   |                          |                                    |                            |                                |
| -                                     |                                         |                                   |                            |                     |                               |                                        |                     |                               |                               |                                        |                                 |                                 |                                      |                                |                              |                                   |                                   |               |                       |               |                      |                                  |                                   |                                    |                                  |                                    |                               |                            |                                     |                                     |                                   |                          |                                    |                            |                                |

|     |         |     |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | the under anoimment diseases (e.g., themmoted antities systemic lipus and conformancials, multiple selectoria and ora selectrice theolow) and immundericiterics (e.g., as excepted below). Additional preferred infeations include a preferred infeations include disorders (such as earlie and drimmanion) inflummation of all mammation inflummation of sesses, e.g., inflummation bowed disease, and conformation of bowed diseases and cookin's diseases), and pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|---------|-----|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 219 | HTABE28 | 603 | Institu Secretion | Assays for measuring secretion of maining are well-known in the art and may be used or routinely modified to the mercenton (title) (to) by peptidies of the mercenton (title) (to) by peptidies of the mercenton (title) (to) by peptidies of the mercenton (title) (to) by peptidies of the mercenton (title) (to) or stumilate measure of the investment by PMAT measurement by Elonsea and also by certain protainely search at many be used or notatively modified to test disruption in a key component in disrepulation is a key component in disruption and also by certain protainely modified to test disruption and the meximum (from pameratic cells) by the properties of the invention (including antibodies and agoniss or disrupting assays disclosed in: Shimini, H., et al. Mel cell Mel cell Mel cell Mel cell Mel cell Mel | A highly preferred indication is diabetes realities. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic reimposphily, diatup disease) (e.g., read failure, nephropathy, diatup disease) (e.g., read failure, nephropathy, diatup disease) (e.g., read failure, nephropathy, diatup disease) (e.g., read failure, nephropathy and condended associated in the "Renal Distorters" and conference in a disease, and conference of e.g., due to disease, and near disease, and conference (e.g., due to disease, and confision, downstring or blood vessel blockage, heart disease, storke, impotence (e.g., due to disease, and more commission, downstrians, mental blockage), sekzures, mental blockage), sekzures, mental blockage), sekzures, mental blockage), sekzures, mental disease, unpercencielyprorsamile rocom, disease, and disease, hypertension, stroke, and other diseases and conference selections in propertices and conference severiments. |

|                                                                                                             |                                                                            |                                                                    | _                               | _                                     | _                                      | _                               | _                                   | _                        | _                                                                          |                                     | _                                | _                                 | _                                  | _                                | _                                | _                                    | _                                                                | _                                      | _                                 | _                                   | _                                  | _                                  | _                                      | _                                   | _                                    | _                                   | _                            | _                                   | _                                   |
|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|--------------------------|----------------------------------------------------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|----------------------------------|----------------------------------|--------------------------------------|------------------------------------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|
| the invention includes a method for stimulating adipocyte differentiation.  An alternative highly preferred | embodiment of the invention<br>includes a method for inhibiting            | adipocyte differentiation. A<br>highly preferred embodiment of the | invention includes a method for | stimulating (e.g., increasing)        | highly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | gur<br>G                 | ampocytes. ruginy preterred<br>indications include endocrine               | disorders (e.g., as described below | under "Endocrine Disorders").    | Highly preferred indications also | include neoplastic diseases (e.g., | lipomas, liposarcomas, and/or as | described below under            | "Hyperproliferative Disorders").     | disorders (e.g. hymertension                                     | congestive heart failure, blood vessel | blockage, heart disease, stroke,  | impotence and/or as described below | under "Immune Activity",           | "Cardiovascular Disorders", and/or | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | under "Neural Activity and   | Neurological Diseases"), and        | infection (e.g., as described below |
| agonists or antagonists of the<br>invention) to promote or inhibit cell<br>proliferation, activation, and   | differentiation. Exemplary assays for ERK kinase activity that may be used | or routinely modified to test ERK<br>kinase-induced activity of    | polypeptides of the invention   | (including antibodies and agonists or | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes | 107(2):126-132 (1999); Nyttakks Jivt,<br>Bjochem Soc Svmp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein         | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these assays are mildick available (e o | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | line that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in | the art.                            |
|                                                                                                             |                                                                            |                                                                    |                                 |                                       |                                        |                                 |                                     |                          |                                                                            |                                     |                                  |                                   |                                    | _                                | _                                |                                      |                                                                  |                                        |                                   | _                                   | _                                  | _                                  | _                                      | _                                   |                                      |                                     |                              | _                                   |                                     |
|                                                                                                             |                                                                            |                                                                    |                                 |                                       |                                        |                                 |                                     |                          |                                                                            |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                                                  |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     |                                     |
|                                                                                                             |                                                                            |                                                                    |                                 |                                       |                                        |                                 |                                     |                          |                                                                            |                                     |                                  |                                   |                                    |                                  |                                  |                                      |                                                                  |                                        |                                   |                                     |                                    |                                    |                                        |                                     |                                      |                                     |                              |                                     | _                                   |

|  | under infections Disease).             |
|--|----------------------------------------|
|  | A highly preferred indication is       |
|  | diabetes mellitus. An additional       |
|  | highly preferred indication is a       |
|  | complication associated with           |
|  | diabetes (e.g., diabetic retinopathy,  |
|  | diabetic nephropathy, kidney disease   |
|  | (e.g., renal failure, nephropathy      |
|  | and/or other diseases and disorders as |
|  | described in the "Renal Disorders"     |
|  | section below), diabetic neuropathy,   |
|  | nerve disease and nerve damage         |
|  | (e.g., due to diabetic neuropathy),    |
|  | blood vessel blockage, heart disease,  |
|  | stroke, impotence (e.g., due to        |
|  | diabetic neuropathy or blood vessel    |
|  | blockage), seizures, mental            |
|  | confusion, drowsiness, nonketotic      |
|  | hyperglycemic-hyperosmolar coma,       |
|  | cardiovascular disease (e.g., heart    |
|  | disease, atherosclerosis,              |
|  | microvascular disease, hypertension,   |
|  | stroke, and other diseases and         |
|  | disorders as described in the          |
|  | "Cardiovascular Disorders" section     |
|  | below), dyslipidemia, endocrine        |
|  | disorders (as described in the         |
|  | "Endocrine Disorders" section          |
|  | below), neuropathy, vision             |
|  | impairment (e.g., diabetic retinopathy |
|  | and blindness), ulcers and impaired    |
|  | wound healing, infection (e.g.,        |
|  | infectious diseases and disorders as   |
|  | described in the "Infectious           |
|  | Diseases" section below (particularly  |
|  | of the urinary tract and skin). An     |
|  | additional highly preferred indication |

|     |         |     |                         |                                         | is obesity and/or complications         |
|-----|---------|-----|-------------------------|-----------------------------------------|-----------------------------------------|
|     |         |     |                         |                                         | associated with obesity. Additional     |
|     |         |     |                         |                                         | highly preferred indications include    |
|     |         |     |                         |                                         | weight loss or alternatively, weight    |
|     |         |     |                         |                                         | gain. Additional highly                 |
|     |         |     |                         |                                         | preferred indications are               |
|     |         |     |                         |                                         | complications associated with insulin   |
|     |         |     |                         |                                         | resistance. Additional highly           |
|     |         |     |                         |                                         | preferred indications are disorders of  |
|     |         |     |                         |                                         | the musculoskeletal systems             |
|     |         |     |                         |                                         | including myopathies, muscular          |
|     |         |     |                         |                                         | dystrophy, and/or as described          |
|     |         |     |                         |                                         | herein. Additional highly               |
|     |         |     |                         |                                         | preferred indications include,          |
|     |         |     |                         |                                         | hypertension, coronary artery           |
|     |         |     |                         |                                         | disease, dyslipidemia, gallstones,      |
|     |         |     |                         |                                         | ostcoarthritis, degenerative arthritis, |
|     |         |     |                         |                                         | eating disorders, fibrosis, cachexia,   |
|     |         |     |                         |                                         | and kidney diseases or disorders.       |
|     |         |     |                         |                                         | Preferred indications include           |
|     |         |     |                         |                                         | neoplasms and cancer, such as,          |
|     |         |     |                         |                                         | lymphoma, leukemia and breast,          |
|     |         |     |                         |                                         | colon, and kidney cancer. Additional    |
|     |         |     |                         |                                         | preferred indications include           |
|     |         |     |                         |                                         | melanoma, prostate, lung,               |
|     |         |     |                         |                                         | pancreatic, esophageal, stomach,        |
|     |         |     |                         |                                         | brain, liver, and urinary cancer.       |
|     |         |     |                         |                                         | Highly preferred indications include    |
|     |         |     |                         |                                         | lipomas and liposarcomas. Other         |
|     |         |     |                         |                                         | preferred indications include benign    |
|     |         |     |                         |                                         | dysproliferative disorders and pre-     |
|     |         |     |                         |                                         | neoplastic conditions, such as, for     |
|     |         |     |                         |                                         | example, hyperplasia, metaplasia,       |
|     |         |     |                         |                                         | and/or dysplasia.                       |
|     | HTECC05 | 625 | Regulation of viability | Assays for the regulation of viability  | A highly preferred indication is        |
| 221 |         |     | and proliferation of    | and proliferation of cells in vitro are | diabetes mellitus. An additional        |
|     |         |     | pancreatic beta cells.  | well-known in the art and may be        | highly preferred indication is a        |

|                                                                            | _                                    | _                                                                           | _                                       | _                                    | _                                | _                                   | _                                     | _                                 | _                                   | _                                   | _                                  | _                                |                                        |                                  |                                       | _                                     | _                                     | _                                    | _                               | _                              | _                                    | _                                   | _                                      | _                                   | _                                       | _                                     | _                                     | _                                            | _                                      | _                                   | _                                     | _                                      | _                                    | _                                    |
|----------------------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------------|----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|---------------------------------|--------------------------------|--------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------------|---------------------------------------|---------------------------------------|----------------------------------------------|----------------------------------------|-------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|
| complication associated with diabetes (e.g., diabetic retinopathy,         | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy<br>and/or other diseases and disorders as | described in the "Renal Disorders"      | section below), diabetic neuropathy, | nerve disease and nerve damage   | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to   | diabetic neuropathy or blood vessel | blockage), seizures, mental         | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart    | discase, atherosclerosis,        | microvascular disease, hypertension,  | stroke, and other diseases and        | disorders as described in the         | "Cardiovascular Disorders" section   | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section        | below), neuropathy, vision          | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g.,     | infectious diseases and disorders as  | described in the "Infectious          | Diseases" section below, especially          | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture). An additional highly    | preferred indication is obesity and/or | complications associated with        | obesity. Additional highly preferred |
| used or routinely modified to assess<br>the ability of polypeptides of the | invention (including antibodies and  | agonists or antagonists of the<br>invention) to regulate viability and      | proliferation of pancreatic beta cells. | For example, the Cell Titer-Glo      | luminescent cell viability assay | measures the number of viable cells | in culture based on quantitation of   | the ATP present which signals the | presence of metabolically active    | cells. Exemplary assays that may be | used or routinely modified to test | regulation of viability and      | proliferation of pancreatic beta cells | by polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Friedrichsen BN, | et al., Mol Endocrinol, 15(1):136-48 | (2001); Huotari MA, ct al.,     | Endocrinology, 139(4):1494-9   | (1998); Hugl SR, et al., J Biol Chem | 1998 Jul 10;273(28):17771-9 (1998), | the contents of each of which is       | herein incorporated by reference in | its entirety. Pancreatic cells that may | be used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ) and/or may be routinely | generated. Exemplary pancreatic        | cells that may be used according to | these assays include rat INS-1 cells. | INS-1 cells are a semi-adherent cell   | line established from cells isolated | from an X-ray induced rat            |
|                                                                            |                                      |                                                                             |                                         |                                      |                                  |                                     |                                       |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                       |                                      |                                 |                                |                                      |                                     |                                        |                                     |                                         |                                       |                                       |                                              |                                        |                                     |                                       |                                        |                                      |                                      |
|                                                                            |                                      |                                                                             |                                         |                                      |                                  |                                     |                                       |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                       |                                      |                                 |                                |                                      |                                     |                                        |                                     |                                         |                                       |                                       |                                              |                                        |                                     |                                       |                                        |                                      |                                      |
|                                                                            |                                      |                                                                             |                                         |                                      |                                  |                                     |                                       |                                   |                                     |                                     |                                    |                                  |                                        |                                  |                                       |                                       |                                       |                                      |                                 |                                |                                      |                                     |                                        |                                     |                                         |                                       |                                       |                                              |                                        |                                     |                                       |                                        |                                      |                                      |

|         |    |                                                 | transplantable insulinoma. These cells retain characteristics typical of native paneratic beta cells including glucose inducible insulin secretion. References: Astric et al. Endocrinology 1992, 130:167.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | indications include weight loss or<br>alternatively, weight gain. Additional<br>highly preferred indications are<br>complications associated with insulin<br>resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| HT6BH92 | 93 | transcription of Malic<br>Enzyme in hepatocytes | transcription of Main Enzyme are wasty for the regulation of the abelian of model-town in the art and ring be used or routinely modified to assess the artification of the art and ring be used or routinely modified to assess in working of melating of properties of the invention (including antibodies of the invention) to regulate transcription of the invention to regulate transcription of the invention to regulate transcription of the invention to regulate transcription of the invention to regulate transcription of the invention of the promoter contains two direct transcription and Med identified as putative PPAR and other transcription along the section of the regulation of transcription and the integration of the regulation of transcription and the regulation of transcription and other transcription and the regulation of transcription disconsists of the invention (including antibodies and environment of the invention) include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed the invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed invention include assays disclosed in a page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page 100 page | A highly preferred indication is diabetes mellitus.  A highly preferred indication is a complication associated with distinction is a complication associated with distinct and proferred indication is a complication associated with diabetic regiments, and subsequently, is directly distorted in the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complication of the complica |

| infections diseases and disorders as secrebed in Particutors. Diseases' section below, especially of the turning treat and skin, carpal turnel syndrome and Duplytoren's orderature). An additional highly preferred infection is obesity. Additional highly preferred infection is obesity and additional sociated with obesity. Additional highly preferred infections independently additional highly preferred alternatively, weight gain. Additional highly preferred infections indications made wight loss or alternatively, weight gain additional highly preferred infections are complications as sociated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | the high preferend indication is obesity and/or complications associated with obesity. Additional highly preferred indication singled world highly preferred indication singled world highly preferred indication singled world highly preferred indication is disheves mellituse. An indication is disheves mellituse. An indication is disheves mellituse. An indication is somplication associated with dishers (e.g., dishelter creinposity), klehvey diseases, e.g. runti lifture, rephropathy, disheves e.g., runtil mitture, rephropathy and/or other diseases and disorders as secried in the Verant Disorders's secried in the Ve |
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| Ilpenberg, A., et al., J Biol Chem, T. (273); 2010(8), 2017 (1997); Berger, et al., Gene 66:1-10 (1988); Berger, et al., Gene 66:1-10 (1988); Berger, et al., Methods in Braymol, 216:362–368 (1992), the Braymol, 216:362–368 (1992), the Braymol, 216:362–368 (1992), the Braymol, 216:362–368 (1992), the Braymol, 216:362–368 (1992), the Braymol, 216:362–368 (1992), the Braymol, 216:362–368 (1992); the Braymol, 216:362–368 (1992); the Braymol, 216:362–368 (1992); the Braymol, 216:362–362 (1992); the Braymol, 216:362–362 (1992); the Braymol, 216:362–362 (1992); the Braymol, 216:362–362 (1992); the Braymol, 216:362 (1992); th | transacription through the cAMP<br>transacription through the cAMP<br>transacription through the cAMP<br>the capture of the control of the<br>the rat and may be used or routinely<br>modified to assess the ability of<br>properplaces of the invention) to<br>modified to assess the ability of<br>including antibodies and agoniss or<br>authorities and the invention) to<br>increase cAMP, regulate CRB<br>increase of AMP, regulate CRB<br>increase of the control of the control<br>increase of the control of the control<br>of the control of the control of the control<br>of the control of the control of the control<br>of the control of the control of the control of the<br>thin adviser the cAMP signaline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| nerne disease and nerne damage     | (e g due to dishetic neuronathy) | blood vessel blockage, heart disease. | stroke, impotence (e.g., due to       | diabetic neuropathy or blood vessel | blockage), seizures, mental        | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma,     | cardiovascular disease (e.g., heart | disease, atherosclerosis,    | microvascular disease, hypertension, | stroke, and other diseases and        | disorders as described in the         | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section        | below), neuropathy, vision      | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious     | Diseases" section below, especially | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's        | contracture). Additional highly      | preferred indications are          | complications associated with insulin | resistance.                         |                                     |                                   |                                          |                                   |                                      |                                 |                              |
|------------------------------------|----------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|------------------------------------|------------------------------------|--------------------------------------|-------------------------------------|------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------------|--------------------------------|--------------------------------------|---------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|----------------------------------------|----------------------------------------|--------------------------------------|------------------------------------|---------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|------------------------------------------|-----------------------------------|--------------------------------------|---------------------------------|------------------------------|
| nathway CREB plays a major role in | adinocenesis and is involved in  | differentiation into adipocytes. CRE  | contains the binding sequence for the | transcription factor CREB (CRE      | binding protein). Exemplary assays | for transcription through the cAMP | response element that may be used or | routinely modified to test cAMP-    | response element activity of | polypeptides of the invention        | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol       | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Reusch et al., Mol Cell   | Biol 20(3):1008-1020 (2000); and    | Klemm et al., J Biol Chem 273:917-  | 923 (1998), the contents of each of  | which are herein incorporated by | reference in its entirety. Pre-     | adipocytes that may be used            | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated. | Exemplary mouse adipocyte cells       | that may be used according to these | assays include 3T3-L1 cells. 3T3-L1 | is an adherent mouse preadipocyte | cell line that is a continuous substrain | of 3T3 fibroblast cells developed | through clonal isolation and undergo | a pre-adipocyte to adipose-like | conversion under appropriate |
|                                    |                                  |                                       |                                       |                                     |                                    |                                    |                                      |                                     |                              |                                      |                                       |                                       |                                    |                                 |                                |                                      |                                 |                                        |                                     |                                     |                                      |                                  |                                     |                                        |                                        |                                      |                                    |                                       |                                     |                                     |                                   |                                          |                                   |                                      |                                 |                              |
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|                                                 | A highly preferred indication is | diabetes mellitus. An             | additional highly preferred indication | is a complication associated with    | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy |                                         | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | _                                   | blockage), seizures, mental    | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart  | disease, atherosclerosis,          | microvascular disease, hypertension, | stroke, and other diseases and      | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine     | disorders (as described in the  | "Endocrine Disorders" section      | below), neuropathy, vision      | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially  | of the urinary tract and skin), carpal |
|-------------------------------------------------|----------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|-----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|--------------------------------|------------------------------------|----------------------------------|--------------------------------------|------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|---------------------------------|------------------------------------|---------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|------------------------------|--------------------------------------|----------------------------------------|
| differentiation conditions known in<br>the art. | Assays for the regulation of     | transcription of Malic Enzyme are | well-known in the art and may be       | used or routinely modified to assess | the ability of polypeptides of the    | invention (including antibodies and  | agonists or antagonists of the    | invention) to regulate transcription of | Malic Enzyme, a key enzyme in      | lipogenesis. Malic enzyme is         | involved in lipogenesisand its | expression is stimulted by insulin. | ME promoter contains two direct       | repeat (DR1)- like elements MEp | and MEd identified as putative PPAR | response elements. ME promoter | may also responds to AP1 and other | transcription factors. Exemplary | assays that may be used or routinely | modified to test for regulation of | transcription of Malic Enzyme (in    | hepatocytes) by polypeptides of the | invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed | in: Streeper, R.S., et al., Mol | Endocrinol, 12(11):1778-91 (1998); | Garcia-Jimenez, C., et al., Mol | Endocrinol, 8(10):1361-9 (1994);       | Barroso, I., et al., J Biol Chem,   | 274(25):17997-8004 (1999);          | Ijpenberg, A., et al., J Biol Chem,  | 272(32):20108-20117 (1997);  | Berger, et al., Gene 66:1-10 (1988); | and. Cullen. B., et al., Methods in    |
|                                                 | Regulation of                    | transcription of Malic            | Enzyme in hepatocytes                  |                                      |                                       |                                      |                                   |                                         |                                    |                                      |                                |                                     |                                       |                                 |                                     |                                |                                    |                                  |                                      |                                    |                                      |                                     |                                     |                                    |                                     |                                 |                                    |                                 |                                        |                                     |                                     |                                      |                              |                                      |                                        |
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|                                                 | HTEFU65                          |                                   |                                        |                                      |                                       |                                      |                                   |                                         |                                    |                                      |                                |                                     |                                       |                                 |                                     |                                |                                    |                                  |                                      |                                    |                                      |                                     |                                     |                                    |                                     |                                 |                                    |                                 |                                        |                                     |                                     |                                      |                              |                                      |                                        |
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| tumnel syndrome and Dignostren's concuerdure). An additional highly preferred indication is obesity and exception associated with obesity. Additional highly preferred indications include wight loss or alternatively, weight gain. Additional highly preferred indications include wight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                        | diabetes, myopathy, muscle cell diabetes, myopathy, muscle cell diabetes, myopathy, muscle cell and of muscle (stoth as, flathdomyoun, and flathdosaroum), centioosacular disorders (stoth as myormas, flromas, congenital myormas, flromas, congenital myormas, flromas, congenital disease, cardine arrest, heart valve disease, cardine fisses, and also as described below tuider disease, weather disease, and also as described below tuider artification, sundianting myoblast proliferation, and inhibiting myoblast proliferation,                                                                                                                                                                             |
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| Enzymol. 216;362–368 (1992), the contents of each of which is herein incorporated by reference in its enterty. Heapweyes that may be used according to these assays are pushed according to these assays are pushed according to these assays are pushed according to these assays are builded by and/or may be outlinely the ATCC**9 and/or may be outlinely the according to these assays included the mouse \$73-1.1 cell line. 313-1, is a mouse \$73-1.1 cell line. 313-1, is a mouse assistant of \$71-1 fline objects of the fline distance of the includence of the adoption. It is a not disposed through deband allowed and the subjects the adoption cell incurrence adoption cell incurrence and according to allowed through a period and prose-like conversion entire appropriate differentiation culture conditions. | are swell known in the art and may be a<br>swell sown in the art and may be a<br>dead or remitting to modified to assess the shilts of rolyperpicts of the inventories (including artibodies and agontists or rangeouses of the inventories) to stimulate or mithin inventories to stimulate or mithin the problest cell profice and the may be used of the proposite of the profice and the may be used of roundinely modified to test entirity of the invention (including agontss or amazonies of the invention) include, for example, useayed disolocated in: for example, useayed disolocated in: costs, C., et all "resustation of the costs ignee in the profiferation of skelelal imuscles of rais" Dave Crownl |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Myoblas cell proliferation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Differ Apr;43(2):155-64 (2001), When Dix, et al. "Gife binding proteins-4, said of may play geodetins-4, said of may play geographic of lost geometry for the proteins-4, said of may play geographic of lost geometry for geometry profileration and differentiation*) I said geometry for the protein of lost geometry (1995), and protein geometry field or beat on proliferation of L6 and field or beat on proliferation of L6 and field or beat on proliferation of L6 and field or beat on proliferation of L6 and field or beat on proliferation of L6 and field or beat on proliferation of L6 and field or beat on proliferation of L6 and field by the contracts of each of which are berein incorporated by reference myoblist cells that may be used are thoughosts L6 cell line. Rea on antherent rat myoblists L6 cell line. Rea on antherent rat myoblists Cell line, sealed from myoblists cell line; solated from myoblists cell line; solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cell mice, solated from myoblists cells are an antherent rat myoblist cells from myoblists myoblists cells mice, solated from myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblists myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist myoblist m | Reporter Assay: construct contains sequence of against and only sequence of squalence synthetises, the first specific argument for decision of the sequence of squalence synthetises, the first specific biosynthetic pathway. See Jung, et al. 1804. Chem. J. 1804. Chem. ASSE 12818-128241(993), the contents of virther biosynthetic pathway. See Jung, et al. 1804. Chem. J. 1804. Chem. See Jung, et al. 1804. See Jung, |
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|                                                                                                     | A highly preferred embodiment for simulating the production of the invention includes a method for simulating the production of embodiment of the invention of embodiment of the invention production of the invention production of the invention production of ThNg. Includes a method for inhibiting the production of ThNg. Includes a method the blood disorders (e.g., set described below disorders (e.g., set described below disorders) (e.g., set described below for a control of the production in the production of infection (e.g., viral infections, infection (e.g., viral infections, infections associated with chronic gramulomaness diseases with chronic gramulomaness diseases with chronic gramulomaness diseases and malignant osserporosis, and/or as described below under "Infections Disease"). Highly preferred diseases (e.g., rheumoid a durinis, specime highs a cythematosis, multiple solerosis and/or as described disease (e.g., rheumoid a durinis, specime bluss evention in the disease disease (e.g., rheumoid a durinis, specime highs a cythematosis, multiple solerosis and/or as described disease (e.g., rheumoid a durinis, specime highs a creptons, and suppressing a T cell-mediated dimmanion and an ill ammatory disearches Additional preferred diseated included immane responses, and suppressing a T cell-mediated dimentions include (editopathic pulmonary) fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnosis. Highly pulmonary fitnos |
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| 209:497-9 (1980), the contents of<br>which are herein incorporated by<br>reference in its entirety. | Friguran HMAT. IPNg ploys a actual role in the immune system and is considered to be a promotion of the immune system and is considered to be a promotion of the immune system and is considered to be a promotion of the immune system in the immune system in the immune system in the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of the immune of Teels. Such assist that may be used or medium the profition of cell-redicted inflammatory activities, modulate inflammatory activities, modulate immune of Teels. Such assays that may be used or coll-rediction of cytokines, such as Interferon gamma (IFNg), assays that may be used or routinely assays that as Interferon gamma (IFNg) assays that may be used or routinely and the activation of cytokines, such as Interferon gamma (IFNg) assays that may be used or routinely assays that may be used or routinely assays that may be used or routinely assays that may be used or routinely assays that may be used or routinely activity of polyperides of the assays that may be used or routinely activity of polyperides of the assays that assays that may be used or routinely activity of polyperides of the assays that are interferon gamma (IFNg).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                     | Production of Froduction of Frogramma using a T cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                     | 627                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                     | ПТВЕТО65                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                     | 223                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Simulation of insulin secretion from paracratic bear cells. | 627 |
|-------------------------------------------------------------|-----|
|-------------------------------------------------------------|-----|

| described in the "Renal Disorders" section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious           | Discases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture). An additional       | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or  | alternatively, weight gain.    | Aditional highly preferred        | indications are complications   | associated with insulin resistance.  |
|-------------------------------------------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|----------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------|---------------------------------|----------------------------------|------------------------------------|----------------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|--------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|-----------------------------------|---------------------------------|--------------------------------------|
| secretion is measured by FMAT using anti-rat insulin antibodies.        | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S et. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | are a semi-adherent cell line        | established from cells isolated from | an X-ray induced rat transplantable | insulinoma. These cells retain | characteristics typical of native | pancreatic beta cells including | glucose inducible insulin secretion. |
|                                                                         |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 |                                      |
|                                                                         |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 |                                      |
|                                                                         |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 |                                      |

|   |         |     |                   | References: Asfari et al.<br>Endocrinology 1992 130:167. |                                        |
|---|---------|-----|-------------------|----------------------------------------------------------|----------------------------------------|
| Ξ | HTEGA76 | 628 | Activation of     | Kinase assay. Kinase assays, for                         | A highly preferred embodiment          |
| _ |         |     | Adipocyte ERK     | example an Elk-1 kinase assay, for                       | of the invention includes a method     |
|   |         |     | Signaling Pathway | ERK signal transduction that regulate                    | for stimulating adipocyte              |
|   |         |     |                   | cell proliferation or differentiation                    | proliferation. An alternative highly   |
|   |         |     |                   | are well known in the art and may be                     | preferred embodiment of the            |
|   |         |     |                   | used or routinely modified to assess                     | invention includes a method for        |
|   |         |     |                   | the ability of polypeptides of the                       | inhibiting adipocyte proliferation.    |
|   |         |     |                   | invention (including antibodies and                      | A highly preferred embodiment of       |
|   |         |     |                   | agonists or antagonists of the                           | the invention includes a method for    |
|   |         |     |                   | invention) to promote or inhibit cell                    | stimulating adipocyte differentiation. |
|   |         |     |                   | proliferation, activation, and                           | An alternative highly preferred        |
|   |         |     |                   | differentiation. Exemplary assays for                    | embodiment of the invention            |
|   |         |     |                   | ERK kinase activity that may be used                     | includes a method for inhibiting       |
| _ |         |     |                   | or routinely modified to test ERK                        | adipocyte differentiation.             |
|   |         |     |                   | kinase-induced activity of                               | highly preferred embodiment of the     |
|   |         |     |                   | polypeptides of the invention                            | invention includes a method for        |
|   |         |     |                   | (including antibodies and agonists or                    | stimulating (e.g., increasing)         |
|   |         |     |                   | antagonists of the invention) include                    | adipocyte activation. An alternative   |
|   |         |     |                   | the assays disclosed in Forrer et al.,                   | highly preferred embodiment of the     |
|   |         |     |                   | Biol Chem 379(8-9):1101-1110                             | invention includes a method for        |
|   |         |     |                   | (1998); Le Marchand-Brustel Y, Exp                       | inhibiting the activation of (e.g.,    |
|   |         |     |                   | Clin Endocrinol Diabetes                                 | decreasing) and/or inactivating        |
|   |         |     |                   | 107(2):126-132 (1999); Kyriakis JM,                      | adipocytes. Highly preferred           |
|   |         |     |                   | Biochem Soc Symp 64:29-48 (1999);                        | indications include endocrine          |
|   |         |     |                   | Chang and Karin, Nature                                  | disorders (e.g., as described below    |
|   |         |     |                   | 410(6824):37-40 (2001); and Cobb                         | under "Endocrine Disorders").          |
|   |         |     |                   | MH, Prog Biophys Mol Biol 71(3-                          | Highly preferred indications also      |
|   |         |     |                   | 4):479-500 (1999); the contents of                       | include neoplastic diseases (e.g.,     |
|   |         |     |                   | each of which are herein                                 | lipomas, liposarcomas, and/or as       |
|   |         |     |                   | incorporated by reference in its                         | described below under                  |
|   |         |     |                   | entirety. Mouse adipocyte cells that                     | "Hyperproliferative Disorders").       |
|   |         |     |                   | may be used according to these                           | Preferred indications include blood    |
| _ |         |     |                   | assays are publicly available (e.g.,                     | disorders (e.g., hypertension,         |
|   |         |     |                   | through the ATCC <sup>TM</sup> ). Exemplary              | congestive heart failure, blood vessel |
|   |         |     |                   | mouse adipocyte cells that may be                        | blockage, heart disease, stroke,       |

| used according to these assays<br>include 3T3-L1 cells. 3T3-L1 is an     | impotence and/or as described below<br>under "Immune Activity",<br>"Cradian Discadar", and/or |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| adherent mouse preadpocyte cen<br>line that is a continuous substrain of | "Blood-Related Disorders"), immune                                                            |
| 3T3 fibroblast cells developed<br>through clonal isolation and undergo   | disorders (e.g., as described below<br>under "Immune Activity"), neural                       |
| a pre-adipocyte to adipose-like                                          | disorders (e.g., as described below                                                           |
| differentiation conditions known in                                      | Neurological Diseases"), and                                                                  |
| the art.                                                                 | infection (e.g., as described below                                                           |
|                                                                          | under "Infectious Disease").                                                                  |
|                                                                          | A highly preferred indication is<br>diabetes mellitus. An additional                          |
|                                                                          | ndica                                                                                         |
|                                                                          | complication associated with                                                                  |
|                                                                          | diabetes (e.g., diabetic retinopathy,                                                         |
|                                                                          | diabetic nephropathy, kidney disease                                                          |
|                                                                          | (e.g., renal failure, nephropathy                                                             |
|                                                                          | described in the "Renal Disorders"                                                            |
|                                                                          | section below), diabetic neuropathy,                                                          |
|                                                                          | nerve disease and nerve damage                                                                |
|                                                                          | (e.g., due to diabetic neuropathy),                                                           |
|                                                                          | blood vessel blockage, heart disease,                                                         |
|                                                                          | diabetic neuropathy or blood vessel                                                           |
|                                                                          | blockage), seizures, mental                                                                   |
|                                                                          | confusion, drowsiness, nonketotic                                                             |
|                                                                          | hyperglycemic-hyperosmolar coma,                                                              |
|                                                                          | cardiovascular disease (e.g., heart                                                           |
|                                                                          | disease, atherosclerosis,                                                                     |
|                                                                          | microvascular disease, hypertension,                                                          |
|                                                                          | Stroke, and other diseases and                                                                |
|                                                                          | "Cardiovascular Disorders" section                                                            |
|                                                                          | below), dyslipidemia, endocrine                                                               |
|                                                                          | disorders (as described in the                                                                |

|  | "Hadoonine Disondere" section                              | action "sadion                                                      |
|--|------------------------------------------------------------|---------------------------------------------------------------------|
|  | t-1                                                        | orders section                                                      |
|  | below), neuropauny, vision<br>inmairment (e.g. diabetic re | betow), neuropauny, vision<br>innairment (e.g. diabetic retinonathy |
|  | and blindness).                                            | and blindness), ulcers and impaired                                 |
|  | wound healing, infection (e.g.,                            | infection (e.g.,                                                    |
|  | infectious disea                                           | infectious diseases and disorders as                                |
|  | described in the "Infectious                               | "Infectious                                                         |
|  | Diseases" section                                          | Diseases" section below (particularly                               |
|  | of the urinary tract and skin).                            | act and skin). An                                                   |
|  | additional highl                                           | additional highly preferred indication                              |
|  | is obesity and/or                                          | is obesity and/or complications                                     |
|  | associated with                                            | associated with obesity. Additional                                 |
|  | highly preferred                                           | highly preferred indications include                                |
|  | weight loss or a                                           | weight loss or alternatively, weight                                |
|  | gain. Addi                                                 | Additional highly                                                   |
|  | preferred indications are                                  | tions are                                                           |
|  | complications a                                            | complications associated with insulin                               |
|  | resistance.                                                | Additional highly                                                   |
|  | preferred indica                                           | preferred indications are disorders of                              |
|  | the musculoskeletal systems                                | letal systems                                                       |
|  | including myop                                             | including myopathies, muscular                                      |
|  | dystrophy, and/or as described                             | or as described                                                     |
|  | herein. Add                                                | Additional highly                                                   |
|  | preferred indications include                              | tions include,                                                      |
|  | hypertension, coronary artery                              | pronary artery                                                      |
|  | disease, dyslipic                                          | disease, dyslipidemia, gallstones,                                  |
|  | osteoarthritis, d                                          | osteoarthritis, degenerative arthritis,                             |
|  | eating disorders                                           | eating disorders, fibrosis, cachexia,                               |
|  | and kidney dise                                            | and kidney diseases or disorders.                                   |
|  | Preferred indications include                              | tions include                                                       |
|  | neoplasms and cancer, such as,                             | cancer, such as,                                                    |
|  | lymphoma, leuk                                             | lymphoma, leukemia and breast,                                      |
|  | colon, and kidne                                           | colon, and kidney cancer. Additional                                |
|  | preferred indications include                              | tions include                                                       |
|  | melanoma, prostate, lung,                                  | tate, lung,                                                         |
|  | pancreatic, esop                                           | pancreatic, esophageal, stomach,                                    |
|  | brain, liver, and urinary cancer.                          | urinary cancer.                                                     |

|     | HTEGA76 | 628 | Endothelial Cell | Caspase Apoptosis. Asservs for                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Highly preferred indications include liponas and liposarcomas. Other preferred indications include benign dyspicients and success and preparation include benign dyspicientive distributions suckes as, for example, hyperplasia, metaplasia, and/or (Saplisia, and/or (Saplisia, Alighly preferred embodiment of Alighly preferred embodiment of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----|---------|-----|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 224 |         | 9   | Approxis         | easpase apoptosis are well known in<br>every exportors in the transmitter of the transmit of<br>modified to assess the ability of<br>modified to assess the ability of<br>modified to assess the ability of<br>modified to assess the ability of<br>promote caspase protease-mediated<br>approvise. Induction of apoptosis in<br>cardothelia cells supporting the<br>with unor regression due to loss of<br>turnor blood sapply. Exemplary<br>with unor regression due to loss of<br>turnor blood sapply. Exemplary<br>be used or routinely modified to test<br>polypeptides of the invention<br>of modern production and appropriate<br>to polypeptides of the invention include<br>polypeptides of the invention include<br>polypeptides of the invention include<br>polypeptides and agonisis or<br>antagoniss of the invention include<br>The PEBS Lett 488(x,3): 122-156 (2000),<br>and Kassan and Herman<br>Atheroscler Through 2(2): 5-80<br>(2000), and Kassan and Herman<br>Atheroscler Through 2(2): 7-80<br>(2000), and Kassan and Herman<br>are better in non-procued by reference<br>may be used according to these<br>assive are publicly available (e.g.,<br>through commercial sources) | the invention includes a method for similarity condominators of a mention includes a method from the invention includes a method from the invention includes an encholar to eligible invention includes an encholar of milhibiting encholarity of the invention includes an enchol for inhibiting preferred embodiment of the preferred embodiment of the simulating enclothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for invention includes a method for invention includes a method of the proferred embodiment of the invention includes a method of the invention includes a method of the invention includes a method of the invention includes a method of milhibiting (e.g., decreasing) apoptoss of endothelial cells. An alternative highly preferred embodiment of the invention includes a method of minhibiting (e.g., decreasing) apoptoss of endothelial endotherent of the invention includes a method of stimulating anapogenisis. An alternative highly preferred embodiment of the invention includes a method of minhibiting angiogenisis. An alternative highly preferred embodiment of the invention includes a method of minhibiting angiogenisis. An alternative highly preferred embodiment of the invention includes a method of minhibiting angiogenisis. An alternative highly preferred embodiment of the invention includes a method of minhibiting angiogenisis. An alternative highly preferred embodiment of the invention includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of principal includes a method of pr |

| invention includes a method for<br>reducing eardiae hyperrophy. An<br>alternative highly preferred<br>embodiment of the invention<br>includes a method for inducing<br>eardiae hyperrophy. Highly                       | preferred indications include<br>propulsati disease; (e.g., as described<br>below under Tipperpolificative<br>booker(s), and disorders of the<br>cardiovascular system (e.g., heart<br>disease, congestive heart failure,<br>hypertension, aorite stenosis,<br>eardiomyopathy, via vuite. | dysfluction, afterwaler and dysfluction, afterwaler and dysfluction, afterwaler disease, additionation afterwaler disease, disheric nephropathy, intracardian distant, cardian plystrophy, mayocardial inferction, chronic myocardial inferction, chronic myocardial inferction, chronic disease, and described below under "Cardiovascular Disorders"). Highly perfect in discions include earthorasemir, erbothelial and/or cardiovascular, cholophilal and/or | angegent desarder (e.g., systemic<br>disorders that affect vessels such as<br>disorders that affect vessels such as<br>delibers milling, sa well is diseases<br>of the vessels themselves, such as of<br>the arteries, capillaries, veins and or<br>the vessels that stimilate<br>indications that similate<br>cardiovascularization. Highly<br>preferred are indications that inhibit<br>angiogenesis and proposed as<br>angiogenesis and public<br>cardiovascularization. Highly<br>cardiovascularization. |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions | that include, but are not limited to, appropriately avacular permeability, vascular tone, and immune cell extravasation.                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|  |   | preferred indications include          |
|--|---|----------------------------------------|
|  |   | antiangiogenic activity to treat solid |
|  |   | tumors, leukemias, and Kaposi"s        |
|  |   | sarcoma, and retinal disorders.        |
|  |   | Highly preferred indications include   |
|  |   | neoplasms and cancer, such as,         |
|  |   | Kaposi"s sarcoma, hemangioma           |
|  |   | (capillary and cavernous), glomus      |
|  |   | tumors, telangiectasia, bacillary      |
|  |   | angiomatosis,                          |
|  |   | hemangioendothelioma,                  |
|  | _ | angiosarcoma,                          |
|  | _ | haemangiopericytoma,                   |
|  | _ | lymphangioma, lymphangiosarcoma.       |
|  |   | Highly preferred indications also      |
|  |   | include cancers such as, prostate,     |
|  | _ | breast, lung, colon, pancreatic,       |
|  |   | esophageal, stomach, brain, liver,     |
|  |   | and urinary cancer. Preferred          |
|  |   | indications include benign             |
|  |   | dysproliferative disorders and pre-    |
|  | _ | neoplastic conditions, such as, for    |
|  |   | example, hyperplasia, metaplasia,      |
|  |   | and/or dysplasia. Highly               |
|  |   | preferred indications also include     |
|  | _ | arterial disease, such as,             |
|  |   | atherosclerosis, hypertension,         |
|  | _ | coronary artery disease,               |
|  |   | inflammatory vasculitides,             |
|  |   | Reynaud"s disease and Reynaud"s        |
|  |   | phenomenom, aneurysms, restenosis;     |
|  |   | venous and lymphatic disorders such    |
|  | _ | as thrombophlebitis, lymphangitis,     |
|  | _ | and lymphedema; and other vascular     |
|  |   |                                        |
|  |   | disease, and cancer. Highly            |
|  |   | preferred indications also include     |

| trauma such as wounds, burns, and | injured tissue (e.g., vascular injury | such as, injury resulting from balloon | angioplasty, and atheroschlerotic | esions), implant fixation, scarring, | schemia reperfusion injury, | rheumatoid arthritis, cerebrovascular | disease, renal diseases such as acute | renal failure, and ostcoporosis. | Additional highly preferred | indications include stroke, graft | rejection, diabetic or other | retinopathies, thrombotic and | coagulative disorders, vascularitis, | lymph angiogenesis, sexual | disorders, age-related macular | degeneration, and treatment | prevention of endometriosis and | related conditions. Additional highly | preferred indications include | fibromas, heart disease, cardiac | dis    | vascular disease. Preferred | indications include blood disorders | (e.g., as described below under | "Immune Activity", "Blood-Related | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications | include autoimmune diseases (e.g., | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below) and | immunodeficiencies (e.g., as | described below). Additional | preferred indications include | inflammation and inflammatory<br>disorders (such as acute and chronic |
|-----------------------------------|---------------------------------------|----------------------------------------|-----------------------------------|--------------------------------------|-----------------------------|---------------------------------------|---------------------------------------|----------------------------------|-----------------------------|-----------------------------------|------------------------------|-------------------------------|--------------------------------------|----------------------------|--------------------------------|-----------------------------|---------------------------------|---------------------------------------|-------------------------------|----------------------------------|--------|-----------------------------|-------------------------------------|---------------------------------|-----------------------------------|------------------------------------|------------------------------------|------------------------------------|--------------------------------------|-----------------------------------|--------------------------------|------------------------------|------------------------------|-------------------------------|-----------------------------------------------------------------------|
| traum                             | injure                                | snch                                   | angio                             | lesion                               | ische                       | rhenr                                 | disea                                 | renal                            | Addit                       | indica                            | reject                       | reting                        | coagu                                | lymb                       | dison                          | deger                       | /brev                           | relate                                | prefer                        | fibroi                           | arrest | vascu                       | indic                               | (e.g.,                          | "Imr                              | Disor                              | Disor                              | inclu                              | rheun                                | eryth                             | and/o                          | imm                          | descr                        | prefe                         | inflat                                                                |
|                                   |                                       |                                        |                                   |                                      |                             |                                       |                                       |                                  |                             |                                   |                              |                               |                                      |                            |                                |                             |                                 |                                       |                               |                                  |        |                             |                                     |                                 |                                   |                                    |                                    |                                    |                                      |                                   |                                |                              |                              |                               |                                                                       |
|                                   |                                       |                                        |                                   |                                      |                             |                                       |                                       |                                  |                             |                                   |                              |                               |                                      |                            |                                |                             |                                 |                                       |                               |                                  |        |                             |                                     |                                 |                                   |                                    |                                    |                                    |                                      |                                   |                                |                              |                              |                               |                                                                       |
|                                   |                                       |                                        |                                   |                                      |                             |                                       |                                       |                                  |                             |                                   |                              |                               |                                      |                            |                                |                             |                                 |                                       |                               |                                  |        |                             |                                     |                                 |                                   |                                    |                                    |                                    |                                      |                                   |                                |                              |                              |                               |                                                                       |

|              |         |     |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | inflammatory diseases, e.g.,<br>inflammatory bowel disease and<br>Crohn's disease), and pain<br>management.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------|---------|-----|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1715<br>1715 | HTEINI3 | 623 | Activation of Adipocyte PRK Signaling Pathway | Kinase assay. Kinase assays, for exemple in IRI. Hismos assay, for TRR signal transluction that regulate of proliferation or officeratiation are well known in the art and may be add or routinely notified to assess the shiliy of polypeptides of the interaction (including antibotics and agonists or anagonists of the or margonists of the differentiation. Exemplary assays for ERK knase excivity that may be used or routinely modified to use IRIK knase excivity that may be used or routinely modified to use IRIK knase excivity that may be used or routinely modified to use IRIK knase excivity of polypeptides of the invention included or routinely modified to use IRIK instanciation and the assay disclosed in Forner et al., Biol Chem 379(8-3); 1101-1110 Cludking antiboties and agonisis or antagonists of the invention include an assay disclosed in Forner et al., Biol Chem 379(8-3); 1101-1110 Cludking antiboties and agony, Kraiskis JM. Brochen Ste Symp 64:29-48 (1999); the contents of each of which are herein end of which are herein entirety. Mouse adioposte cells that entirety. Mouse allocating to these assass are entiriety available (e.e. | A highly preferred embodiment of the invention includes a method for stimulating adaptory to estimulating adaptory profileration. A stiffly preferred embodiment of the invention includes a method for inhibiting adaptory epoileration. An alermative highly preferred embodiment of the invention includes a method for embodiment of the invention includes a method for inhibiting adaptory edifferentiation. A highly preferred embodiment of the invention includes a method for inhibiting adaptory at amendo for inhibiting the adaptivation of (e.g., increasing) adaptory as artivation. An alternative includes a method for invention includes a method for intention includes a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for a method for individual for an admitted for a subartered indications also individual for a hyperproliferative Disorders?). |

| congestive heart failure, blood vessel blockage, heart disease, stroke, impotrese and/or as described below under "Immune Activity", "Cardiovascular Diseaders", and/or "Disead Dated Diseaders", inseed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | disorders (e.g., as described below<br>made "Immano Activity"), nearla<br>disorders (e.g., as described below<br>disorders (e.g., as described below<br>mader "Neural Activity") and<br>Neurological Diseases"), and<br>Neurological Diseases"), and<br>infection (e.g., as described below<br>under "Infections Diseases"), and<br>dishefens mellins. An additional<br>dishebers mellins. An additional<br>profile preferred indecation is<br>complication associated with<br>dishept preferred indecation with<br>dishepts of the profile of the profile of the<br>dishers (e.g., dishect) extensionally.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | action to appropriate and action to account or propropriate and account or propropriate and account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account of account |
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| through the ATCC <sup>13</sup> ). 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|  | below), dyslipidemia, endocrine         |
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|  | disorders (as described in the          |
|  | "Endocrine Disorders" section           |
|  | below), neuropathy, vision              |
|  | impairment (e.g., diabetic retinopathy  |
|  | and blindness), ulcers and impaired     |
|  | wound healing, infection (e.g.,         |
|  | infectious diseases and disorders as    |
|  | described in the "Infectious            |
|  | Diseases" section below (particularly   |
|  | of the urinary tract and skin). An      |
|  | additional highly preferred indication  |
|  | is obesity and/or complications         |
|  | associated with obesity. Additional     |
|  | highly preferred indications include    |
|  | weight loss or alternatively, weight    |
|  | gain. Additional highly                 |
|  | preferred indications are               |
|  | complications associated with insulin   |
|  | resistance. Additional highly           |
|  | preferred indications are disorders of  |
|  | the musculoskeletal systems             |
|  | including myopathies, muscular          |
|  | dystrophy, and/or as described          |
|  | herein. Additional highly               |
|  | preferred indications include,          |
|  | hypertension, coronary artery           |
|  | disease, dyslipidemia, gallstones,      |
|  | osteoarthritis, degenerative arthritis, |
|  | eating disorders, fibrosis, cachexia,   |
|  | and kidney diseases or disorders.       |
|  | Preferred indications include           |
|  | neoplasms and cancer, such as,          |
|  | lymphoma, leukemia and breast,          |
|  | colon, and kidney cancer. Additional    |
|  | preferred indications include           |
|  | melanoma, prostate, lung,               |

| HTEJN13 225 HTELP17 | NI3 | 629 | Inhibition of squatere transcription.  Transcription.  Regulation of transcription through the EPCK promoter in hepatocytes | Reporter Assay: construct contains regulatory and coding sequence of canadiancy surfaces, the first specific enzyme in the cholesterol enzyme in the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and the cholesterol and t | herine til seguggett sommer, benin, liver, and urinary cancer, bening and lipseaconass, other lipomas and lipseaconas, other lipomas and lipseaconas, other proprietive disorders and prevented indications; such as, for example, hypothesis, metaphasia, metaphasia, and/or dysplasia.  A highly preferred indication is a disabette very administration of the perferred indication is a complesion associated with disabette organical metaphasia, and/or dysplasia.  A highly preferred indication is a complesion or security and cancer of the perferred indication is a complesion or security with disabetic unphoppilly, iddived six-associated with diabetic unphoppilly, iddived six-associated with diabetic unphoppilly, iddived six-associated with the perfect or appropriate property or security and security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or security or s |
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|                     |     |     |                                                                                                                             | (including antibodies and agonists or<br>antagonists of the invention) to<br>activate the PEPCK pomoter in a<br>reporter construct and regulate liver<br>gluconcogenesis. Exemplary assays                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | (e.g., renal failure, nephropathy<br>and/or other diseases and disorders as<br>described in the "Renal Disorders"<br>section below), diabetic neuropathy,<br>nerve disease and nerve damate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| (e.g., due to diabetic neuropathy),<br>blood vessel blockage, heart disease,<br>stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel | blockage), seizures, mental<br>confusion, drowsiness, nonketotic<br>hyperglycemic-hyperosmolar coma,         | cardiovascular disease (e.g., heart<br>disease, atheroselerosis,<br>microvascular disease, hypertension,<br>stroke, and other diseases and                                      | unsotuces as described in the<br>"Cardiovascular Disorders" section<br>below), dyslipidemia, endocrine<br>disorders (as described in the<br>"Endocrine Disorders" section            | below), neuropathy, vision<br>impairment (e.g., diabetic retinopathy<br>and blindness), ulcers and impaired<br>wound healing, infection (e.g., an<br>infectious diseases or disorders as<br>described in the "Infectious         | Diseases' section below, especially of the uninary treat and skin), carpal turned syndrome and Dupuyren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or | alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the miscilications are disorders of the |
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| for regulation of transcription<br>through the PEPCK promoter that<br>may be used or routinely modified to<br>test for PEPCK promoter activity (in     | hepatocytes) of polypeptides of the<br>invention (including antibodies and<br>agonists or antagonists of the | invention) include assays disclosed in<br>Berger et al., Gene 66:1-10 (1998);<br>Cullen and Malm, Methods in<br>Enzymol 216:362-368 (1992);<br>Handwar et al. Deco Mat Acad Sci | Trention et a., Troc Ivan Acad Sci<br>USA 85:6342-6346 (1988).<br>Lochhead et al., Diabetes 49(6):896-<br>903 (2000), and Yeagley et al., J Biol<br>Chem 275(23):17814-17820 (2000), | the contents of each of which is herein incorporated by reference in is entirely. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC <sup>28</sup> ) and/or may be used. | routinely generated. Exemplary liver phenators cells that may be used according to these assays include HHE cells, whith contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.                                                                                                                                                       |                                                                                                                                                                                                                            |
|                                                                                                                                                        |                                                                                                              |                                                                                                                                                                                 |                                                                                                                                                                                      |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                            |
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| 226 | нтырту | 059 | Stimulation of Calcium<br>Flux in puncreatic beta<br>cells. | are veel known in the art and may be used to routinely modified to assess the balliot of polypeptides of the mivertion (including antibodies and university of polypeptides of the invention) to mobilize seldum. For any other polypeptides of the invention to mobilize seldum. For asset may be used to measure influx of cleatium. For a concentrations of cytosolic calcium conventrations f calcium, Extracellular calcium. Extracellular calcium, Extracellular calcium, Extracellular calcium, Extracellular calcium, expiration of calcium, popular calcium, postura calcium in calcium casars sciantifica in may be used or routinely modified to may be used or routinely modified to functioning antibodies and agoniss or automatorial or functioning antibodies and agoniss or automation for the recursion include assays disclosed in: Saint LS, et al., [1995], McGaurison SB, et al., Cell (1995), McGaurison SB, et al., Cell (1992), and Meats, JR, et al., Cell (1993), the contents of casol or viviled. | A highly predienced indication is diabetes mellitus.  A highly proferred indication is a complexes mellitus additional highly perceived indication is a complexes of e.g., dishectic retinopality, dates of disease the distances of e.g., dishectic retinopality, is a complexes of e.g., dishectic retinopality, is a complexed to e.g., cent distances and disease and aberve diseases and disease and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases and aberve diseases. See the disease is mental eight of the diseases and aberve diseases, amental containing, drowsiness, mental condition, drowsiness, mental conditions, drowsiness, and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseases and diseas |

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Panevenic cells that may be used according to these assays are publicly available (e.g., through the ATCC***) and/or may be continely accorded by the public powersance cells that may be used according to cells that may be used according to cells that may be used according to the sawsy include IHIT15 cells. HIT15 are an adherent epithetial cells that may be used according to the cashing cell from Syrian harmaser islet cells transformed with harmaser islet cells transformed with harmaser islet cells transformed with examinestic and glucocordioid receptors. The cells secrete insulin, which is stimulated by glucose and supressed by                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Diseases' section below, expecially of the unimary read and skin), carpal turned syndrome and Dapuyteen is contractured. An additional futured syndrome succession of the unimary read of the unimary read and skin), carpal turned syndrome is a social deviation of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of the unimary of |
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| HTELS08 | 189 | Regulation of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the | USA 78: 4394443, 1981.  Assays for the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulation of the regulatio | A highly preferred indication is diabetes racilities. An additional highly preferred indication is action from the complexity of the complexity associated with diabetes (e.g., diabetic repiropolatyly, kidney disease (e.g., renal failure, rephropolatyly kidney disease) (e.g., renal failure, rephropolatyly kidney disease) (e.g., renal failure, rephropolatyly kidney disease) and described in the "Renal Disorders as section below), diabetic neuropathy, extra disease and alter ved famage (e.g., due to diabetic neuropathy), diabetic neuropathy, and diabetic neuropathy and sease that disease, after the sease of the complexity of diabetic neuropathy of sease of sease of the complexity of those descriptions and diabetic neuropathy or blood vessel choices.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| confusion, drowsiness, nonketotic<br>hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart    | disease, atherosclerosis,           | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine      | disorders (as described in the         | "Endocrine Disorders" section    | below), neuropathy, vision       | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., an | infectious diseases or disorders as  | described in the "Infectious      | Diseases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's   | contracture). An additional           | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Additional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred | indications are disorders of the | musculoskeletal systems including | myopathies, muscular dystrophy, | and/or as described herein. | Additional highly preferred | indications include glycogen storage | disease (e.g., glycogenoses), |
|-----------------------------------------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|------------------------------------|--------------------------------------|----------------------------------------|----------------------------------|----------------------------------|----------------------------------------|-------------------------------------|------------------------------------|--------------------------------------|-----------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|---------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------|----------------------------------|-----------------------------------|---------------------------------|-----------------------------|-----------------------------|--------------------------------------|-------------------------------|
| invention (including antibodies and agonists or antagonists of the    | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in          | Enzymol 216:362-368 (1992);    | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988);           | Lochhead et al., Diabetes 49(6):896- | 903 (2000); and Yeagley et al., J Biol | Chem 275(23):17814-17820 (2000), | the contents of each of which is | herein incorporated by reference in    | its entirety. Hepatocyte cells that | may be used according to these     | assays are publicly available (e.g., | through the ATCCTM) and/or may be | routinely generated. Exemplary liver | hepatoma cells that may be used        | according to these assays include | H4lle cells, which contain a tyrosine | amino transferase that is inducible    | with glucocorticoids, insulin, or    | cAMP derivatives.                    |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                      |                               |
|                                                                       |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                      |                               |
|                                                                       |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                      |                               |
|                                                                       |                                        |                                     |                                      |                                |                                     |                                    |                                      |                                        |                                  |                                  |                                        |                                     |                                    |                                      |                                   |                                      |                                        |                                   |                                       |                                        |                                      |                                      |                                    |                             |                             |                               |                                     |                             |                                  |                                   |                                 |                             |                             |                                      |                               |

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| Reporter Assay, construct contains against and coling sequence of squalater synthesise, the first specific program in the closistened biosynthesis palments, the first specific biosynthesis palments, 288 12818.  128241(993), the contents of which we herein more threat morphometric by reference in its entirety, Cells were treated with SID supermisting, and SLAP activity was measured after 72 hours carcinoma cell line (ATCC* HB-1905), Sec Roberts of 1890, the contents of 299497-9 (1980), the contents of 299497-9 (1980), the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the contents of the | chapter Appropries are well known in caspace upoptosis are well known in the far and map be used or nontinely modified to assess the ability of polypeptides of the invention of polypeptides of the invention) to managonists of the invention) to promote caspace protease-mediated apoptosis. Induction of apoptosis in the approprie to the approprie of the proposition of apoptosis in the approprie to the approprie to the approprie to the approprie to the approprie to the approprie to the approprie to the invention of apoptosis and the properties of the invention of including antibodies and agoniss or espace apoptosis activity of including antibodies and agoniss or disclosed in Lee et al., the assays disclosed in Lee et al.,                                                                                                                                                                                                                                                                              |
| Inhibition of squatene gone transcription.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Apoptosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 199                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 632                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| HTELS08                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | нтыруз                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 227                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 228                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| HEBS Lett 485(2.3); 122-126 (2000); Nor et al., J. Vabe 88; 7(5); 292-18 (2000); and Karsan and Harim. J. Advenseder Thront 3(2); 75-80 (1996); the contents of each of which are better incorporated by reference in its entirety. Endothelial calls that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be taken docuring in othese assays include borize endothelial cells that may be an endothelial sources). Exemplary endothelial cells that may be an endothelial cells that may be an endothelial controlled to the seasons include borize and cells that may be an endothelial controlled in the blood vessels and are involved in functions that include, but with this blood vessels and are involved in functions that include, but with this blood vessels and are involved in functions of angelogenesis, viscular premientific, viscular rome and immune cell extravasation. | includes a method for inhibiting (e.g., decreasing) papopass of endothetial cells.  A highly preferred condition in includes in method for stimulating in method for stimulating perferred embodiment of the inhibiting angiogensis. A highly preferred conditionant of the inhibiting angiogenesis and preferred embodiment of the inhibiting angiogenesis. A highly preferred conditionant of the invention includes a method for inhibiting angiogenesis. A highly preferred conditions of the invention includes a method for andacting earlies highly preferred intensions include and includes a method for andacting or and alternative highly preferred in includes in method for andacting earlies highly preferred in includes a method for andacting earlies highly preferred in facilities in the proposition of the invention in the conditions include morphistic diseases; (e.g., is described bissistic diseases; (e.g., is described diseases; congestive heart failune, endicionary oppuly, valvular diseases, congestive heart failune, endicionary oppulation alternosiclensis and distinction  |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | dishrone-brondic vescular disease, dishrone-brondic vescular disease, dishrone-brondic vescular dispersophy, intraendine shunt, cardine hypertrophy, noverthal infraction, chronic hemodynamic overloud, and/or as described below most include vescular bloom was include earthorouse include cardiovascular Disorders"). Highly perfect disdications is include cardiovascular, cardothelial mullor cardiovascular, cardothelial mullor disorders that affect vessels such as disorders that affect vessels such as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| disheves neitling, as well as diseasess of the verseis themselves, such as of the arteries copiliaries, veries and or Juraphatics). Highly preferred are indications that stimulate are indications that stimulate are indications to a magiogenesis and or cardiovascalarization. Highly preferred are indications that inhibit ampiogenesis and or cardiovascalarization. Highly preferred indications include annuanginganic activity to treat solid tumons, tearfer indications include annuanginganic activity to treat solid tumons, tearfer indications include monoplasms and carden, said its Kaposi's servora, burnangiona (caphilary and exercine), glomus umons, telangucchasia, bacillary and exercinesis, bacillary and exercinesis, bacillary and exercinesis, bacillary and exercinesis, bacillary and ampiocration, and an area and an area and all the preferred indications also humangior-doubdisiona.  Highly preferred indications also |
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| incilude concers such as, prostate, breast, lung, colon, paracreatic, esophageal, sommel, breai, liver, and luniary cancer. Preferred indications include benign obsportificative discueders and pre-receptable by preparations, and as for example, hyperplasia, neutaplasia, audiout or spatial and preferred indications also include artered indications also include and entitle disease, such as, altherosolerosis, hypertension, and attentions, and attention and attentions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|  | assessib metre menonon                 |
|--|----------------------------------------|
|  | inflammatory meanlisdae                |
|  | Revnand"s disease and Revnand"s        |
|  | phenomenom, aneurysms, restenosis;     |
|  | venous and lymphatic disorders such    |
|  | as thrombophicbitis, lymphangitis,     |
|  | and lymphedema; and other vascular     |
|  | disorders such as peripheral vascular  |
|  | disease, and cancer. Highly            |
|  | preferred indications also include     |
|  | trauma such as wounds, burns, and      |
|  | injured tissue (e.g., vascular injury  |
|  | such as, injury resulting from balloon |
|  | angioplasty, and atheroschlerotic      |
|  | lesions), implant fixation, scarring,  |
|  | ischemia reperfusion injury,           |
|  | rheumatoid arthritis, cerebrovascular  |
|  | disease, renal diseases such as acute  |
|  | renal failure, and osteoporosis.       |
|  | Additional highly preferred            |
|  | indications include stroke, graft      |
|  | rejection, diabetic or other           |
|  | retinopathies, thrombotic and          |
|  | coagulative disorders, vascularitis,   |
|  | lymph angiogenesis, sexual             |
|  | disorders, age-related macular         |
|  | degeneration, and treatment            |
|  | /prevention of endometriosis and       |
|  | related conditions. Additional highly  |
|  | preferred indications include          |
|  | fibromas, heart disease, cardiac       |
|  | arrest, heart valve disease, and       |
|  | vascular disease. Preferred            |
|  | indications include blood disorders    |
|  | (e.g., as described below under        |
|  | "Immune Activity", "Blood-Related      |
|  | Disorders", and/or "Cardiovascular     |

| Disnotersy). Preferred indications include autoimmus diseases (e.g., rheumond artifuits, systemic lupus expremanous, multiple sedencia indicate described below) and immunodeficiates (e.g., as described below). Additional inflammanoty diseases, e.g., inflammanoty sistems, neglectured indications include inflammanoty diseases, e.g., inflammanoty bessesses, e.g., inflammanoty bevel diseases, e.g., cohin s'etissesse, g.a., cohin s'etissesse, and pain management. | A preferred rendericant of the invention includes a method for includes an embod for includes an embod for includes an embod for includes an embod for simulating (e.g., rectaining) TMF alpha embodies on an embod for simulating and collection includes an embod for simulating production. Preferred indications includes before the production and production and production and production and production and production and production and production and production and production and production and production and production and production and production and production and production and production and arthritis, floodes systemic lupts a systemic lupts a systemic lupts a systemic lupts a production and or a described below). Immuno engotic and experimental production and or a described below). Immuno engotics, and mediated immune response, and immu |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Assays for the activation of transacription through the Serum ment Response Elements (SRE) are well-known in the art and may be used or known in the art and may be used or hopographics of the invention for londuing anthodics and agonists or antagonists of the invention for londuing anthodics and agonists or antagonists of the invention for the actual properties of the invention for the actual properties of the invention for the actual properties of the invention of genes involved in growth. Exemplary assays for transcription through the SRE that transcription through the SRE that transcription through the SRE that managements of the polypeptides and agonists or amagonists of the polypeptides and agonists or amagonists of the following the SRE actual and Maham, Methods in Berger et al., Gene 661-10 (1998); Erzymol 216:562-568 (1989).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Advivation of Advivation of Advivation of transcription through summarune response element in immune echis (such as T-cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 632                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HTLEP\$3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 228                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Black et al., Virus Genes 12(2):105-<br>117 (1997), the content of each of | preferred indications include inflammatory |
|----------------------------------------------------------------------------|--------------------------------------------|
| which are herein incorporated by                                           | disorders, and treating joint damage       |
| reference in its entirety. T cells that                                    | in patients with rheumatoid arthritis.     |
| may be used according to these                                             | An additional highly preferred             |
| assays are publicly available (e.g.,                                       | indication is sepsis. Highly               |
| through the ATCC <sup>140</sup> ). Exemplary                               | preferred indications include              |
| mouse T cells that may be used                                             | neoplastic diseases (e.g., leukemia,       |
| according to these assays include the                                      | lymphoma, and/or as described              |
| CTLL cell line, which is an IL-2                                           | below under "Hyperproliferative            |
| dependent suspension culture of T                                          | Disorders"). Additionally, highly          |
| cells with cytotoxic activity.                                             | preferred indications include              |
|                                                                            | neoplasms and cancers, such as, for        |
|                                                                            | example, leukemia, lymphoma,               |
|                                                                            | melanoma, glioma (e.g., malignant          |
|                                                                            | glioma), solid tumors, and prostate,       |
|                                                                            | breast, lung, colon, pancreatic,           |
|                                                                            | esophageal, stomach, brain, liver and      |
|                                                                            | urinary cancer. Other preferred            |
|                                                                            | indications include benign                 |
|                                                                            | dysproliferative disorders and pre-        |
|                                                                            | neoplastic conditions, such as, for        |
|                                                                            | 3                                          |
|                                                                            | and/or dysplasia. Preferred                |
|                                                                            | indications include anemia,                |
|                                                                            | pancytopenia, leukopenia,                  |
|                                                                            | thrombocytopenia, Hodgkin's                |
|                                                                            | disease, acute lymphocytic anemia          |
|                                                                            | (ALL), plasmacytomas, multiple             |
|                                                                            | myeloma, Burkitt's lymphoma,               |
|                                                                            | arthritis, AIDS, granulomatous             |
|                                                                            | discase, inflammatory bowel disease,       |
|                                                                            | neutropenia, neutrophilia, psoriasis,      |
|                                                                            | suppression of immune reactions to         |
|                                                                            | transplanted organs and tissues,           |
|                                                                            | hemophilia, hypercoagulation,              |
|                                                                            | diabetes mellitus, endocarditis,           |

| meningitis, I.yme Disease, cardine reperlision iijuv, and sahmma and allergy. An additional preferred indication is infection (e.g., an infections disease as described below funder "Infections Disease"). | Assays for measuring section of minetian revel-known in the art and minetian revel-known in the art and the art and revenued or morphism to assay the ability of polypoptics of the invention (mohiling unthoding multiple and gening is a consistent of the invention (mohiling unthoding and gening is measured by PMAI securion in pattern of the invention of summation in subjects of the invention of mohiling in the invention of mohiling in the invention of maintain secretion from a managemists of the invention of maintain secretion from summation of maintain secretion from part of the invention of maintain secretion from the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from part of the invention of maintain secretion from the invention of maintain secretion from the invention of th |
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|                                                                                                                                                                                                             | Insulin Secretion Assays for Insulin zee we a may be used assays for Insulin zee we may be used assays and the invention of secretion. It is supplied to the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the |
|                                                                                                                                                                                                             | 632                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| _                                                                                                                                                                                                           | HTLEP5 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| infectious diseases and disorders as been being the frietedous Diseases* section below, copeculity for the unitary term and skin, carpal turned syndrome and Duptytern's contracture). An additional highly preferred indication is obesity and complications associated with obesity. Additional highly preferred indications includencing indications include weight loss or alternatively, weight gain. Additional alternatively, weight gain. Additional alternatively, weight gain. Additional resistance, complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | allegy, stefan, and rhintis, allegy, stefan, and rhintis, allegy, staffun, and rhintis, additional preference includes include infection (e.g., an infections include infection (e.g., an infections breazes, as described below under "Interestions Dresses"), and inflammatory and inflammatory include blood disorders. Reference infections also include blood disorders (e.g., as exercible the bown under "Immune Activity", 180och Related and Activity", 180och Related Disorders, and Disorders, and city cardiocations in Professional and Professional and arthritis, systemic brusan, cleaness (e.g., rheumatoid arthritis, systemic brusa. |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cach of which is breven incorporated by reference in its entirey. Paracreaic cells that may be used according to these assays are publicly available (e.g., through the ATCCP <sup>3</sup> ). Exemplary pancreaic cells that may be used excording to these assays include HITTIS Cells. HITTIS and address or pictured in the master is the address or pictured in the address or pictured in the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is the address or picture is a simulated by glusose and glusomotions. ATTC# (REL-177) and suppressed to semanterial or and picture is the address or picture is simulated by glusose and glusomotions. It is simulated by glusose and glusomotions. It is simulated by glusose and glusomotions. It is addressed to the address of the address or picture is a simulated by glusose and glusomotions. It is simulated by glusose and glusomotions. It is addressed to the address of the addressed to the address of the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed to the addressed | activation of the GATA-3 signating activation of the GATA-3 signating plans which are the GATA-3 signating and advanced to the GATA-3 signating and advanced to the GATA-3 in mass reaches the seven linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA steepones chemotic the activation of transcription modified to assess the ability out modified to assess the ability out from the activation of the invention of (including antibodies and agonists or amagonists of the invention) to regulate CATA-3 transcription factors.                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | transcription through of<br>transcription through<br>Text. 3 response<br>clement in immune<br>cells (each as must<br>cells).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 632                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | нтир53                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 228                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| erythematosis, multiple sclerosis<br>and/or as described below) and<br>immunodeficiencies (e.g., as              | described below). Preferred indications include neoplastic              | diseases (e.g., leukemia, lymphoma,<br>melanoma, prostate, breast, lung, | colon, pancreatic, esophageal,<br>stomach, brain, liver, and urinary   | tract cancers and/or as described<br>below under "Hynermoliferative       | Disorders"). Other preferred    | indications include benign | dyspronicranye disorders and pre-<br>neoplastic conditions, such as, for | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred | indications include anemia,   | pancytopenia, leukopenia,     | thrombocytopenia, leukemias,       | Hodgkin's disease, acute            | lymphocytic anemia (ALL),           | plasmacytomas, multiple myeloma,     | burkiu s iymphoma, artmrus, ALDS,<br>granilomatoris disease, inflammatory | bowel disease, sepsis, neutropenia,   | ncutrophilia, psoriasis, suppression   | of immune reactions to transplanted | organs and tissues, hemophilia,            | hypercoagulation, diabetes mellitus, | endocarditis, meningitis, and Lyme  | Disease.                         |                                     |                                    |                                  |                                  |             |
|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------|----------------------------|--------------------------------------------------------------------------|-----------------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|---------------------------------------------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------------|--------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|------------------------------------|----------------------------------|----------------------------------|-------------|
| and modulate expression of mast cell<br>genes important for immune response<br>development. Exemplary assays for | transcription through the GATA3<br>response element that may be used or | routinely modified to test GATA3-<br>response element activity of        | polypeptides of the invention<br>(including antibodies and agonists or | antagonists of the invention) include<br>assays disclosed in Beroer et al | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol   | 216:362-368 (1992); Hendrom et al.,<br>Proc Natl Acad Sci USA 85:6342-   | 6346 (1988); Flavell et al., Cold | Spring Harb Symp Quant Biol | 64:563-571 (1999); Rodriguez- | Palmero et al., Eur J Immunol | 29(12):3914-3924 (1999); Zheng and | Flavell, Cell 89(4):587-596 (1997); | and Henderson et al., Mol Cell Biol | 14(6):4286-4294 (1994), the contents | ot each of which are neverily<br>incomporated by reference in its         | entirety. Mast cells that may be used | according to these assays are publicly | available (e.g., through the        | ATCC <sup>1M</sup> ). Exemplary human mast | cells that may be used according to  | these assays include the HMC-1 cell | line, which is an immature human | mast cell line established from the | peripheral blood of a patient with | mast cell leukemia, and exhibits | many characteristics of immature | mast cells. |
|                                                                                                                  |                                                                         |                                                                          |                                                                        |                                                                           |                                 |                            |                                                                          |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                                                           |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |                                    |                                  |                                  |             |
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|                                                                                                                  |                                                                         |                                                                          |                                                                        |                                                                           |                                 |                            |                                                                          |                                   |                             |                               |                               |                                    |                                     |                                     |                                      |                                                                           |                                       |                                        |                                     |                                            |                                      |                                     |                                  |                                     |                                    |                                  |                                  |             |

| Highly preferred indications include | allergy, asthma, and rhinitis.   | Additional preferred indications | include infection (e.g., an infectious | disease as described below under      | "Infectious Disease"), and       | inflammation and inflammatory   | disorders. Preferred indications also | include blood disorders (e.g., as | described below under "Immune     | Activity", "Blood-Related    | Disorders", and/or "Cardiovascular | Disorders"). Preferred indications | include autoimmune diseases (e.g.,    | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis   | and/or as described below) and   | immunodeficiencies (e.g., as | described below). Preferred     | indications include neoplastic | diseases (e.g., leukemia, lymphoma,  | melanoma, prostate, breast, lung, | colon, pancreatic, esophageal, | stomach, brain, liver, and urinary | tract cancers and/or as described     | below under "Hyperproliferative       | Disorders"). Other preferred       | indications include benign      | dysproliferative disorders and pre- | neoplastic conditions, such as, for  | example, hyperplasia, metaplasia, | and/or dysplasia. Preferred        | indications include anemia,        | pancytopenia, leukopenia,     | thrombocytopenia, leukemias, | Hodgkin's disease, acute         | lymphocytic anemia (ALL),        |
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| This reporter assay measures         | activation of the NFAT signaling | pathway in HMC-1 human mast cell | line. Activation of NFAT in mast       | cells has been linked to cytokine and | chemokine production. Assays for | the activation of transcription | through the Nuclear Factor of         | Activated T cells (NFAT) response | element are well-known in the art | and may be used or routinely | modified to assess the ability of  | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) to     | regulate NFAT transcription factors | and modulate expression of genes | involved in immunomodulatory | functions. Exemplary assays for | transcription through the NFAT | response element that may be used or | routinely modified to test NFAT-  | response element activity of   | polypeptides of the invention      | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in Berger et al., | Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol            | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342-   | 6346 (1988); De Boer et al., Int J | Biochem Cell Biol 31(10):1221-1236 | (1999); Ali et al., J Immunol | 165(12):7215-7223 (2000);    | Hutchinson and McCloskey, J Biol | Chem 270(27):16333-16338 (1995), |
| Activation of                        | transcription through            | NFAT response                    | element in immune                      | cells (such as mast                   | cells).                          |                                 |                                       |                                   |                                   |                              |                                    |                                    |                                       |                                      |                                     |                                  |                              |                                 |                                |                                      |                                   |                                |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |
| 632                                  |                                  |                                  |                                        |                                       |                                  |                                 |                                       |                                   |                                   |                              |                                    |                                    |                                       |                                      |                                     |                                  |                              |                                 |                                |                                      |                                   |                                |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |
| HTLEP53                              |                                  |                                  |                                        |                                       |                                  |                                 |                                       |                                   |                                   |                              |                                    |                                    |                                       |                                      |                                     |                                  |                              |                                 |                                |                                      |                                   |                                |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |
|                                      | 228                              |                                  |                                        |                                       |                                  |                                 |                                       |                                   |                                   |                              |                                    |                                    |                                       |                                      |                                     |                                  |                              |                                 |                                |                                      |                                   |                                |                                    |                                       |                                       |                                    |                                 |                                     |                                      |                                   |                                    |                                    |                               |                              |                                  |                                  |

| plasmacytomus, multiple myelomu,<br>arkital i sympou, arkitals, AIDS,<br>gramiorancios disease, inflammatory<br>wowed disease, gassis, neuropenia,<br>neurophilia, isonisis, suprossion<br>cimmar readicius to transplanted<br>organs and itsues, hemophilia,<br>hyperoagulation, disbetes mellins,<br>endocarditis, memiglis, and Lyme<br>Disease.                                                                                                                                                                                                                                     | Highly preferred indications include endocrine disorders (e.g., as executed below under "Endocrine Disorders") and disorders of the Disorders") and disorders of the Disorders") and disorders of the Preferred indications include "Preferred indications include proposition disorders (e.g., as described below under "Immuse "Hyperproliferative"). Is bond disorders (e.g., as described below under "Immuse Activity", "cardiovascular Activity", "cardiovascular Disorders"), Immune disorders (e.g., as described below under "Immuse Activity"), narunt disorders (e.g., as described below under "Immuse Activity"), narund disorders (e.g., as described below under "Immuse Activity"), narund disorders (e.g., as described below under "Imcletion (e.g., as described below under "Imcletion (e.g., as described below under "Imcletion (e.g., as described below inder "Imcletion (e.g., as described below inder "Imcletion (e.g., as described below inder "Infection (e.g., as described below inder "Infection (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infections (e.g., as described below inder "Infecti |
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| and Turner et al., J Exp Med each of Whish the contents of each of Whish are bretin each of Whish are bretin enorograded by reference in its entirety. Mast cells that may be used entirety. Mast cells that may be used enoroging to these assays are publicly available (e.g., through the available (e.g., through the may be used according to line, which is an immanze human mast cell line, switch as mirranter human mast cell line, soft a patient with mast cell leskermi, and exhibits many characteristics of immature many characteristics of immature mast cell leskermi, | items assay, from the assays, for cramplek IEI-i kinnee assays, for the Ke signal transaction that regulate cell positive from the assay and the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the assay of the arrention to promote or inhici cell provident and assay of the arrention of the assay of the arrention of the arrention and the arrention and the arrention and the arrention and the arrention and the arrention and the arrention and the arrention included to the arrention of the arrention include the arrention include the assay of sichosed in Forner et al. (1998), Le Marchand-Britaly I Et p                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Anderstan of Skeletal Massel Cell ERK Signalling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 229                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic      | nephropathy, kidney disease (e.g.,<br>renal failure, nephropathy and/or<br>other diseases and disorders as<br>described in the "Renal Disorders" | section below), diabetic neuropathy,<br>nerve disease and nerve damage<br>(e.g., due to diabetic neuropathy),<br>blood vessel blockage, heart disease, | stroke, impotence (e.g., due to<br>diabetic neuropathy or blood vessel<br>blockage), seizures, mental<br>confusion, drowsiness, nonketotic                | hyperglycemic-hyperosmolar coma,<br>cardiovascular disease (e.g., heart<br>disease, atheroselerosis,              | microvascular disease, hypertension,<br>stroke, and other diseases and<br>disorders as described in the | "Cardiovascular Disorders" section<br>below), dyslipidemia, endocrine<br>disorders (as described in the<br>"Endocrine Disorders" section | below), neuropathy, vision<br>impairment (e.g., diabetic retinopathy<br>and blindness), ulcers and impaired | wound nearing, intection (e.g., infectious diseases and disorders as described in the "Infectious diseases" specifical price of the proposed specifical policy are proposed to the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control | Diseases section below, especiary of the urinary tract and skin), carpal turnel syndrome and Dupuytren's contracture). An additional highly melerred indication is obsestiv |
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| Clin Endocrinol Diabetes<br>107(2):126-132 (1999); Kyriakis JM,<br>Biochem Soc Symp 64:29-48 (1999);<br>Chang and Karin, Nature | 410(6824);37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4);479-500 (1999); the contents of each of which are herein                      | incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the     | ALCL <sup>18</sup> ). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, | isolated from primary cultures of rat<br>thigh muscle, that fuses to form<br>multinucleated myotubes and striated | nbers after culture in differentiation<br>media.                                                        |                                                                                                                                          |                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                             |
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| agonist    | agonists or antagonists of the               | diabetic nephropathy, kidney disease   |
|------------|----------------------------------------------|----------------------------------------|
| inventic   | invention) to mobilize calcium. For          | (e.g., renal failure, nephropathy      |
| example    | example, the FLPR assay may be               | and/or other diseases and disorders as |
| ot besu    | used to measure influx of calcium.           | described in the "Renal Disorders"     |
| Cells no   | Cells normally have very low                 | section below), diabetic neuropathy,   |
| concent    | concentrations of cytosolic calcium          | nerve disease and nerve damage         |
| compar     | compared to much higher                      | (e.g., due to diabetic neuropathy),    |
| extrace    | extracellular calcium. Extracellular         | blood vessel blockage, heart disease,  |
| factors    | factors can cause an influx of               | stroke, impotence (e.g., due to        |
| calcium    | calcium, leading to activation of            | diabetic neuropathy or blood vessel    |
| calcium    | calcium responsive signaling                 | blockage), seizures, mental            |
| pathwa     | pathways and alterations in cell             | confusion, drowsiness, nonketotic      |
| function   | functions. Exemplary assays that             | hyperglycemic-hyperosmolar coma,       |
| may be     | may be used or routinely modified to         | cardiovascular disease (e.g., heart    |
| measur     | measure calcium flux by                      | disease, atherosclerosis,              |
| bolyper    | polypeptides of the invention                | microvascular disease, hypertension,   |
| (includi   | (including antibodies and agonists or        | stroke, and other diseases and         |
| antagon    | antagonists of the invention) include        | disorders as described in the          |
| assays     | assays disclosed in: Satin LS, et al.,       | "Cardiovascular Disorders" section     |
| Endocri    | Endocrinology, 136(10):4589-601              | below), dyslipidemia, endocrine        |
| (1995);    | (1995);Mogatni H, et al.,                    | disorders (as described in the         |
| Endocri    | Endocrinology, 136(7):2960-6                 | "Endocrine Disorders" section          |
| (1995);    | (1995); Richardson SB, et al.,               | below), neuropathy, vision             |
| Biocher    | Biochem J, 288 ( Pt 3):847-51                | impairment (e.g., diabetic retinopathy |
| (1992);    | (1992); and, Meats, JE, et al., Cell         | and blindness), ulcers and impaired    |
| Calciun    | Calcium 1989 Nov-Dec;10(8):535-41            | wound healing, and infection (e.g.,    |
| (1989),    | (1989), the contents of each of which        | infectious diseases and disorders as   |
| is herei   | is herein incorporated by reference in       | described in the "Infectious           |
| its entir  | its entirety. Pancreatic cells that may      | Diseases" section below, especially    |
| pen aq     | be used according to these assays are        | of the urinary tract and skin), carpal |
| publich    | publicly available (e.g., through the        | tunnel syndrome and Dupuytren's        |
| ATCC       | ATCC <sup>TM</sup> ) and/or may be routinely | contracture). An additional            |
| generati   | generated. Exemplary pancreatic              | highly preferred indication is obesity |
| cells that | cells that may be used according to          | and/or complications associated with   |
| these as   | these assays include HITT15 Cells.           | obesity. Additional highly preferred   |
| HITTI      | HITT15 are an adherent epithelial            | indications include weight loss or     |
| cell line  | cell line established from Syrian            | alternatively, weight gain.            |

| Aditional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                       | highly preferred influsions is in the highly preferred influsions in the highly preferred influsions and an experimental interaction is a complication ussociated influence of experimentally, in the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property |
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| humster islet cells transformed with<br>840°th These cells cryptes gluegon,<br>sornatostalin, and glutocouricoid<br>receptors. The cells searche insulin,<br>which is simulated by glucose and<br>gluegous and suppressed by<br>sornatostalin or glucocorricoids.<br>THC (EVLL-TTT Reds: Lord and<br>Ashorott. Biochem. 2, 219–547–551.<br>USA 78: 433–4434; 1981. | stayes for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the shifty of polyperides of the irrention (including amadonises of the irrention functioning analogous of the irrention for simulate insulin secretion). For example, issulin secretion for semple, issulin secretion for simulate insulin secretion for simulate insulin secretion from parceasible has a least in successive by the signature of the superplace, and least to predict the secretion from parceasible has by certain proteins/peptides, and also by certain proteins/peptides, and calls supergulated by medified to test for mination of insulin secretion (functioning authorities and agouists or leading authorities and agouists or (including authorities and agouists or leading authorities and agouists or leading authorities and agouists or sample one in Shiman, III, et al. Landord, 147(2):261.94 (2000); Salaparde, A.M., et al., Mol. V. A.cad. Shimane, A.M., et al., Mol. V. A.cad. Fillsson, & et al., Ann. V. A.cad.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                    | Insulin Sceretion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                                                                                                                                                                                                                                                                                                                                    | 635                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                                                                                                                                                                                                                                                                                                                                                    | 231                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| HTSEW17 636 Su see | Simulation of insulin<br>secretion from<br>panceatic beta cells. | each of which is herein incorporated by Checkness of Fereine in season are publicly according to these assess are publicly avoiding to the season are publicly avoiding to the season are publicly avoiding to the season are publicly and or may be routinely generated. The formularly penerated cells that may be used according to these assays are publicly and the publicly and adherent cythelial cell line and adherent cythelial cell line and adherent cythelial cell line and adherent cythelial cell line cells transformed with SV40. These and adherent cythelial cell line cells transformed with SV40. These season is allowed as a SV Syrian hamedra is all although the season of the season and suppressed by sommoratin or glucocordicoids. A TICH of CRL 1777 Refs. Lott and Asheord. Buscher et al. Proc. 1921 5447-551. Statemer et al. Proc. Natl. Acad. Sci. USA 783-4439-444. Assays for measuring secretorion of may be used or routinely modified to fine revenition furthing amproprise of a present invarient producting a present and publicly of the removaling accordicion of may be used or routinely modified to | infections diseases and disection (e.g., infections diseases and diseases and diseases and diseases and diseases and diseases aschied in the "Infections Diseases" section helow, especially to the inmay rate and skin), carpul turned syndrome and Japayoren's contracture). An additional highly preferred infection is noticed with fair preferred infections include weight loss or another and according and additional highly preferred infections include weight loss or another another and additional highly preferred infections are complications associated with insulin resistance.  A highly preferred indication is additional highly preferred indication is active sensition.  A highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication is additional highly preferred indication in the preferred indication is additional highly preferred indication in the preferred indication is additional highly preferred indication in the preferred indication is additional highly preferred indication in the preferred indication is additional highly preferred indication in the preferred indication is additional preferred indication in the preferred indication is additional preferred indication in the preferred indication in the preferred indication in the preferred indication in the preferred indication in the preferred indication in the preferred indication in the prefer |
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|                    |                                                                  | and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| _                  |                                                                  | using anti-rat insulin antibodies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | section below), diabetic neuropathy,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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| control discount and a control democratic |                                   | (e.g., ture to made to nemobattly),<br>blood vessel blockage, heart disease. | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | discase, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious           | Diseases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture). An additional       | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or  | alternatively, weight gain.    | Aditional highly preferred        | indications are complications   | associated with insulin resistance.  |                           |                             |
| Inclin connection from monocortic hoto    | msum secretion nom parcicale octa | also by certain proteins/pentides, and                                       | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S ct. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | are a semi-adherent cell line        | established from cells isolated from | an X-ray induced rat transplantable | insulinoma. These cells retain | characteristics typical of native | pancreatic beta cells including | glucose inducible insulin secretion. | References: Asfari et al. | Endocrinology 1992 130:167. |
|                                           | _                                 |                                                                              |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 | _                                |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        | _                                   |                                   |                                        | _                                    |                                      | _                                   |                                | _                                 |                                 |                                      |                           |                             |
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|                              | <ul> <li>invention include using polypeptides<br/>nown in of the invention (or antibodies,</li> </ul> | _                                    | Ť                                 | _                             | onists or Autoimmunity, Allergy and Asthma | ) to                             | 1 factors                           |                            |                         | ription                            | element                           | All A                          | onse                           | ides of                             | bodies                              | of the                             | sclosed                             |                               | Pyatt                           |                               | erger et                           | ullen and                            |                          | om et al.,                           | :6342-                          | z et al,                           | (1997);                          | TP .                        | raser et                            | nc nc                          | e herein                             | its                              | may be                             | ys are                             | neh the                               |
|------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------|-----------------------------------|-------------------------------|--------------------------------------------|----------------------------------|-------------------------------------|----------------------------|-------------------------|------------------------------------|-----------------------------------|--------------------------------|--------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|-------------------------------|---------------------------------|-------------------------------|------------------------------------|--------------------------------------|--------------------------|--------------------------------------|---------------------------------|------------------------------------|----------------------------------|-----------------------------|-------------------------------------|--------------------------------|--------------------------------------|----------------------------------|------------------------------------|------------------------------------|---------------------------------------|
| Assays for the activation of | transcription through the NFKB response element are well-known in                                     | the art and may be used or routinely | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or      | antagonists of the invention) to | regulate NFKB transcription factors | and modulate expression of | immunomodulatory genes. | Exemplary assays for transcription | through the NFKB response element | that may be used or rountinely | modified to test NFKB-response | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed | in: Gri G, et al., Biol Chem, | 273(11):6431-6438 (1998); Pyatt | DW, et al., Cell Biol Toxicol | 2000;16(1):41-51 (2000); Berger et | al., Gene 66:1-10 (1998); Cullen and | Malm, Methods in Enzymol | 216:362-368 (1992); Henthorn et al., | Proc Natl Acad Sci USA 85:6342- | 6346 (1988); Valle Blazquez et al, | Immunology 90(3):455-460 (1997); | Aramburau et al., J Exp Med | 82(3):801-810 (1995); and Fraser et | al., 29(3):838-844 (1999), the | contents of each of which are herein | incorporated by reference in its | entirety. Immune cells that may be | used according to these assays are | publicly available (e.g., through the |
| Activation of                | transcription through<br>NFKB response                                                                | element in immune                    | cells (such as B-cells).          |                               |                                            |                                  |                                     |                            |                         |                                    |                                   |                                |                                |                                     |                                     |                                    |                                     |                               |                                 |                               |                                    |                                      |                          |                                      |                                 |                                    |                                  |                             |                                     |                                |                                      |                                  |                                    |                                    |                                       |
| 636                          |                                                                                                       |                                      |                                   |                               |                                            |                                  |                                     |                            |                         |                                    |                                   |                                |                                |                                     |                                     |                                    |                                     |                               |                                 |                               |                                    |                                      |                          |                                      |                                 |                                    |                                  |                             |                                     |                                |                                      |                                  |                                    |                                    | _                                     |
| HTSEW17                      |                                                                                                       |                                      |                                   |                               |                                            |                                  |                                     |                            |                         |                                    |                                   |                                |                                |                                     |                                     |                                    |                                     |                               |                                 |                               |                                    |                                      |                          |                                      |                                 |                                    |                                  |                             |                                     |                                |                                      |                                  |                                    |                                    |                                       |
|                              | 232                                                                                                   |                                      |                                   |                               |                                            |                                  |                                     |                            |                         |                                    |                                   |                                |                                |                                     |                                     |                                    |                                     |                               |                                 |                               |                                    |                                      |                          |                                      |                                 |                                    |                                  |                             |                                     |                                |                                      |                                  |                                    |                                    |                                       |

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| ATCC <sup>IM</sup> ). Exemplary immune cells that may be used according to these assays include the Reh B-cell line. | insulin are well-known in the art and meaning accretion of meaning accretion of a sease by a substitute of meaning and the art and meaning well-known in the art and meaning well-known in the art and meaning well-known in the invention of insuling accretion. For example, insulin accretion for example, insulin accretion from a sease and a sease of the invention of simulation insuling meaning malerial manipolicies. Insulin accretion from pancaetic else tupegalidates, and also by certain proteins/poptides, and else is upregulated by glucose and also by certain proteins/poptides, and else is upregulated by glucose and also by certain proteins/poptides, and else is upregulated by a company fatter and proteins of its impregulated in a seasy situation of itsulin secretion for simulation of itsulin secretion for simulation of itsuling accretion include assays disclosed in Ahran, B. et al., Enderdmobig, and Amelian Sept. 18, 71(2), 233-9. (1999), it. M., et al., Endermobig. 18, 22-04 (1999), the contents of each of which is herein incorporated and of which is herein incorporated the analyse is easily accounted the calls that may be used available (e.e. through the ATCCPA).                             |
|                                                                                                                      | Similation of insulin secucion from pracreatic beta cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| An additional standard and additional standard and additional dication is obesity as associated with all highly preferred weight loss or the gain.  The gain control of the gain control of the gain control of the gain and the gain and the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain control of the gain con | An highly preferred indication is eese mellims.  A highly preferred indication is inclined highly perferred indication complication associated with eese (e.g., dathetic retinopathy, etc. (e.g., dathetic retinopathy, etc. (e.g., dathetic retinopathy, etc. or other dissuess and disorders as incled in the "Renal Disorders" as freed in the "Renal Disorders" and existent better to emange of existent posture to existent disease, and there are any existent disease, and existent disease, in mental existent disease (e.g., then the "Renal Properors and are comparable to existent and existent diseases of the preferred in the control of the diseases and other diseases and existent diseases and existent diseases existent of existent diseases and existent diseases and existent diseases and eventual placenters section                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| or the urinary net and skill, carpal<br>turnel syndrome and Dappyters) accounteautro. An additional<br>highly preferred indication is obesity<br>and or complications associated with<br>obesity. Additional highly preferred<br>indications minde weight loss or<br>indications and the weight some<br>additional highly preferred<br>indications are complications<br>associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | diabetes mellins.  A highly preterned indicato is idealetes mellins.  Bediational lightly preferred indication is a complication associated with clarkets complication associated with clarkets (e.g., diabetic reclinopathy, kidnog disease (e.g., renal failure, nephropathy and mode other diseases and disoaders as described in the "Renal Disoaders" sector helow), albette memopathy, nerve diseases and merve damage (e.g., there indicates and merve damage except helow), albette memopathy, belood vessel blockage, heart disease, and the confliction complexity, and confliction compatibly or blood vessel blockage, hearters, mental confliction, drowsiness, monited confliction, drowsiness, monited disease, and disease, and disease, in pherenasion, stroke, and other diseases, and diseases, and diseases, and diseases, and defenditions described in the "Cardiovascular Disorders" section ("Cardiovascular Disorders" section.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| below), dyslipidemia, endocrine<br>diswerders (a ekesznebel in the<br>diswerders (a ekesznebel in the<br>"Handocrine Diswerders" section<br>below), neuropathy, vision<br>impariment (e.g., diabetic retinopathy<br>and blindness), ludess and impaired<br>wound healine and infection (e.g. | described in the "Infections as described in the "Infections described in the "Infections described in the "Infections described in the "Infections of the uniony treat and skin), cample the uniony treat and skin), cample owners street, and a distributional brighty preferred indications associated with indications in softward with the "Infections associated with indications in softward with the "Infections indications indications in softward with a street of the "Infections in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infection in Infec | Androin inguis prefer et indications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Highly preferred indications include inflammation (caucia and chronic), resmost, atherosclerosis, sathma and allergy, Highly preferred indications include inflammation and inflammatory disorders, commentation and disorders, contect inflammatical and disorders, contect inflammatical disorders, and disorders (e.g., cancer/tumorispensis). |
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| invention) include assays disclosed<br>in Sirveper, R.S., et al., Mol<br>Endocrinol, 12(11):1778-91 (1985);<br>Garcia-Jimene, C., et al., Mol<br>Endocrinol, 8(10):1361-9 (1994);<br>Barnoso, I., et al., J Biol Chem,<br>274255-17997-8004 (1999).                                          | 272(23)-2010(4-2017 (logar)<br>272(23)-2010(4-2017 (logar)<br>gregor ct al., Grobe 66-1-01 (1988;<br>and, Cullen, B. et al., Methods in<br>and, Cullen, B. et al., Methods in<br>contrars of each of which is logar,<br>the contrars of each of which is logar<br>contrars of each of which is logar<br>entroy. Highwayer that may be<br>entroy. Highwayer that may be<br>notified to these assoys are<br>publicly available (e.g., flunggli the<br>ACC <sup></sup> ), and or may be contractly                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | the general. Teaching to these season in the may be used according to these seasy includes the mouse 713-L1 cell line. 373-L1 is a mouse the mode of the cell line. 373-L1 is a mouse in eachipoyee de line (adherent). It is a continuous substrain of 3713 filt having a general mouse and in the cell line (adherent). It is a continuous substrain of 3713 filt having a continuous substrain of 3713 filt having a continuous substrain of 3713 filt having a continuous substrain de substrain of 3713 filt having a continuous substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substrain de substra | Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including ambodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT                                                                   |
|                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Production of VCAM<br>in endothelial cells<br>(such as human<br>umbilical vein<br>endothelial cells<br>(HUVEC))                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 639                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HTWKE60                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 235                                                                                                                                                                                                                                                                                                                                               |

| and cardiorascular disorders (such as described below mode "mmune Activity", "Blood keland Daviers," Histord keland Disorders," Histord keland Disorders," Histord keland Disorders, "Indip preferred indications include neoplasms and accuracy such as, for example, indeed indications include neoplasms and enter eld carcinoma, and prostate, lettermin, Jurphorna, mad prostate, bereasi, lung, colon, puncreatic, capabiguels, acoma, henin, liver and unimary cancer. Other preferred indications include benigm dispositive classifications disculative disarders and preparative disarders and preparative disarders and preparative disarders and precurantly hyperplasts, metaplasts, and of dysplasts.                                                                                                                                                                                                                                                                                     | A highly preferred emboliment<br>of the invention includes a method<br>for simulating approprie<br>profileration. An alternative highly<br>preferred emboliment of the<br>intibiting adjato-ye proliferation.<br>The profileration includes a method for<br>intibiting adjato-ye proliferation.<br>The properties of the properties of the<br>intention includes a method for<br>maintaining adjacency telliferation.<br>An alternative highly preferred<br>and alternative highly preferred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| mun by e used to meanre the cupression in ordotelate cells. Explorition of cell surface VCAM-1 cupression in ordotelate cells. Endotheliate (cells are cells that line blood vessels, and are involved in minutous falls indución blan indución blan indución blan indución blan indución blan indución blan indución blan indución de la matematicida, vascular none, and manume cell extravasation immune cell extravasation indución la culta fant may be usued necordina cells fant may be usued necordina cells (HUVEC), which manche benedicial cells (HUVEC), which was waitable from commercial sources. The expression of VCAM sourchases de curravasation of ymphocytes, leucocytes and other manume cells inom blood vessels; hus VCAM expression plays as role inflammanto cells nombious de curravasation of ymphocytes, leucocytes and other immune cells inombiot yet extravasation of ymphocytes, leucocytes and other in promotyting international and such inflammanto cells nomania. | the continue assay, for the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common and the common a |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Activation of<br>Adipocyte ERK<br>Signaling Pathway                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 640                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HTXAJ12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| -                                 | e E                                                                   |                                       | tive                                  | the                                    |                                 |                                     |                                 | p                                   |                                   | W                                   |                                  | 0                                 | _                                  |                                 |                                  |                                      | poc                                 |                                      | essel                                  |                                   | elow                                |                                    | l/or                               | mme                                   | W                                   | al                                   | W                                   |                              |                                     | M.                                  |                              |                                  | onal               |                                  |
|-----------------------------------|-----------------------------------------------------------------------|---------------------------------------|---------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|------------------------------------|---------------------------------|----------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------|------------------------------------|------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|--------------------|----------------------------------|
| ion. A                            | nignty preserved embodiment of the<br>invention includes a method for | easing)                               | adipocyte activation. An alternative  | nighly preferred embodiment of the     | invention includes a method for | inhibiting the activation of (e.g., | activating                      | Highly preferred                    | ndocrine                          | disorders (e.g., as described below | sorders").                       | Highly preferred indications also | include neoplastic diseases (e.g., | ipomas, liposarcomas, and/or as | T.                               | "Hyperproliferative Disorders")      | Preferred indications include blood | tension,                             | congestive heart failure, blood vessel | se, stroke,                       | impotence and/or as described below | vity",                             | 'Cardiovascular Disorders", and/or | 'Blood-Related Disorders"), immune    | disorders (e.g., as described below | under "Immune Activity"), neural     | disorders (e.g., as described below | ty and                       | s"), and                            | infection (e.g., as described below | ease").                      | A highly preferred indication is | An additional      | cation is a                      |
| adipocyte differentiation.        | ierrea emb                                                            | stimulating (e.g., increasing)        | activation.                           | ferred emb                             | includes a                      | the activati                        | decreasing) and/or inactivating |                                     | indications include endocrine     | e.g., as des                        | inder "Endocrine Disorders").    | ferred indi                       | oplastic dis                       | posarcoma                       | described below under            | liferative I                         | indications                         | disorders (e.g., hypertension,       | heart failt                            | olockage, heart disease, stroke,  | and/or as                           | inder "Immune Activity",           | scular Disc                        | slated Diso                           | e.g., as des                        | mune Activ                           | e.g., as des                        | under "Neural Activity and   | Neurological Diseases"), and        | e.g., as des                        | under "Infectious Disease"). | referred in                      | ellitus.           | highly preferred indication is a |
| adipocyte                         | invention                                                             | stimulatin                            | adipocyte                             | highly pre                             | invention                       | inhibiting                          | decreasing                      | adipocytes.                         | indication                        | disorders                           | under "En                        | Highly pre                        | include ne                         | lipomas, l                      | described                        | "Hyperpro                            | Ргебетер                            | disorders                            | congestive                             | blockage,                         | impotence                           | under "Im                          | "Cardiova                          | "Blood-Re                             | disorders                           | under "Im                            | disorders                           | under "Ne                    | Neurologi                           | infection (                         | under "Inf                   | A highly r                       | diabetes mellitus. | highly pre                       |
| ERK                               |                                                                       | onists or                             | include                               | r et al.,                              | 01                              | 1 Y, Exp                            |                                 | akis JM,                            | 3 (1999);                         |                                     | Cobb                             | 71(3-                             | nts of                             |                                 | its                              | ells that                            | se                                  | (e.g.,                               | nplary                                 | ay be                             | s/                                  | I is an                            | cell                               | train of                              | 2                                   | undergo                              | ke                                  |                              | own in                              |                                     |                              |                                  |                    |                                  |
| ied to test                       | uvuy or<br>e inventior                                                | ies and ag                            | invention)                            | ed in Forre                            | 11-1011:(6                      | and-Bruste                          | iabetes                         | 999); Kyri                          | ip 64:29-48                       | Nature                              | 2001); and                       | s Mol Biol                        | ; the conte                        | herein                          | ference in                       | dipocyte c                           | ding to the                         | y available                          | лм). Ехеп                              | cells that m                      | these assay                         | ils. 3T3-L                         | eadipocyte                         | sqns snon                             | s develope                          | lation and                           | adipose-li                          | appropriate                  | ditions kn                          |                                     |                              |                                  |                    |                                  |
| or routinely modified to test ERK | kmase-induced activity of<br>polynentides of the invention            | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Forrer et al., | Biol Chem 379(8-9):1101-1110    | (1998); Le Marchand-Brustel Y, Exp  | Clin Endocrinol Diabetes        | 107(2):126-132 (1999); Kyriakis JM, | Biochem Soc Symp 64:29-48 (1999); | Chang and Karin, Nature             | 410(6824):37-40 (2001); and Cobb | MH, Prog Biophys Mol Biol 71(3-   | 4):479-500 (1999); the contents of | each of which are herein        | incorporated by reference in its | entirety. Mouse adipocyte cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM). Exemplary         | mouse adipocyte cells that may be | used according to these assays      | include 3T3-L1 cells. 3T3-L1 is an | adherent mouse preadipocyte cell   | ine that is a continuous substrain of | 3T3 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like     | conversion under appropriate | differentiation conditions known in |                                     |                              |                                  |                    |                                  |
| or routi                          | nolvnen                                                               | (includi                              | antagon                               | the assa                               | Biol Ch                         | (1998);                             | Clin En                         | 107(2):                             | Biocher                           | Chang 8                             | 410(682                          | MH, Pp                            | 4):479-                            | each of                         | incorpo                          | entirety                             | may be                              | assays a                             | through                                | mouse                             | nsed ac                             | include                            | adheren                            | line tha                              | 3T3 fib                             | through                              | a pre-ad                            | convers                      | differen                            | the art.                            |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |
|                                   |                                                                       |                                       |                                       |                                        |                                 |                                     |                                 |                                     |                                   |                                     |                                  |                                   |                                    |                                 |                                  |                                      |                                     |                                      |                                        |                                   |                                     |                                    |                                    |                                       |                                     |                                      |                                     |                              |                                     |                                     |                              |                                  |                    |                                  |

| diabetes (e.g., diabetic retinopathy, | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below (particularly | of the urinary tract and skin). An | additional highly preferred indication | is obesity and/or complications | associated with obesity. Additional | highly preferred indications include | weight loss or alternatively, weight |
|---------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------------------|----------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|------------------------------|---------------------------------------|------------------------------------|----------------------------------------|---------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|
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| described in the "Renal Disorders" section below) diabetic neuronathy | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental    | confusion, drowsiness, nonketotic  | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart  | discase, atherosclerosis,          | microvascular disease, hypertension, | stroke, and other diseases and      | disorders as described in the       | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine     | disorders (as described in the  | "Endocrine Disorders" section      | below), neuropathy, vision      | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially  | of the urinary tract and skin), carpal | me a                             | contracture). An additional         | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or    | alternatively, weight gain.     | Aditional highly preferred       | indications are complications       | associated with insulin resistance. |
|-----------------------------------------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|--------------------------------|------------------------------------|----------------------------------|--------------------------------------|------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|---------------------------------|------------------------------------|---------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|------------------------------|--------------------------------------|----------------------------------------|----------------------------------|-------------------------------------|----------------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|---------------------------------|----------------------------------|-------------------------------------|-------------------------------------|
| Malic Enzyme, a key enzyme in<br>linoenesis Malic enzyme is           | involved in lipogenesisand its | expression is stimulted by insulin. | ME promoter contains two direct       | repeat (DR1)- like elements MEp | and MEd identified as putative PPAR | response elements. ME promoter | may also responds to AP1 and other | transcription factors. Exemplary | assays that may be used or routinely | modified to test for regulation of | transcription of Malic Enzyme (in    | hepatocytes) by polypeptides of the | invention (including antibodies and | agonists or antagonists of the     | invention) include assays disclosed | in: Streeper, R.S., et al., Mol | Endocrinol, 12(11):1778-91 (1998); | Garcia-Jimenez, C., et al., Mol | Endocrinol, 8(10):1361-9 (1994);       | Barroso, I., et al., J Biol Chem,   | 274(25):17997-8004 (1999);          | ljpenberg, A., et al., J Biol Chem,  | 272(32):20108-20117 (1997);  | Berger, et al., Gene 66:1-10 (1988); | and, Cullen, B., et al., Methods in    | Enzymol. 216:362-368 (1992), the | contents of each of which is herein | incorporated by reference in its       | entirety. Hepatocytes that may be    | used according to these assays are   | publicly available (e.g., through the | ATCCTM) and/or may be routinely | generated. Exemplary hepatocytes | that may be used according to these | assays includes the mouse 3T3-L1    |
|                                                                       |                                |                                     |                                       |                                 |                                     |                                |                                    |                                  |                                      |                                    |                                      |                                     |                                     |                                    |                                     |                                 |                                    |                                 |                                        |                                     |                                     |                                      |                              |                                      |                                        |                                  |                                     |                                        |                                      |                                      |                                       |                                 |                                  |                                     |                                     |
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| HTXKF95 642 | cell line. 313-L1 is a mouse preadpooyte cell line (adhecen). It is a continuous sabarani of 313 fishoohasa developed through closul isolation. Cells indege a pre- adipooyte to adjoose-like contension under apporpiate differentiation culture conditions. | Advivation of Steletal  Massic cettal  Kinnes assays, for rightly preferred indications and standard of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the con |
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|             |                                                                                                                                                                                                                                                               | HTXKF95                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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| section below), diabetic neuropathy, | _                                     | _                                     | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to              | diabetic neuropathy or blood vessel | blockage), seizures, mental          | confusion, drowsiness, nonketotic   | hyperglycemic-hyperosmolar coma,      | cardiovascular disease (e.g., heart | Ť                                    | microvascular disease, hypertension,    | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section | below), neuropathy, vision | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired | wound healing, infection (e.g., | infectious diseases and disorders as | described in the "Infectious | Diseases" section below, especially | of the urinary tract and skin), carpal | me | contracture). An additional | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or | alternatively, weight gain. | Aditional highly preferred | indications are complications | associated with insulin resistance. | Additional highly preferred |
| incorporated by reference in its     | entirety. Rat myoblast cells that may | be used according to these assays are | publicly available (e.g., through the | ATCC <sup>TM</sup> ). Exemplary rat myoblast | cells that may be used according to | these assays include L6 cells. L6 is | an adherent rat myoblast cell line, | isolated from primary cultures of rat | thigh muscle, that fuses to form    | multinucleated myotubes and striated | fibers after culture in differentiation | media.                         |                               |                                    |                                 |                                |                               |                            |                                        |                                     |                                 |                                      |                              |                                     |                                        |    |                             |                                        |                                      |                                      |                                    |                             |                            |                               |                                     |                             |
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| 239 | HTXON32 | 643 | Insulin Secretion | insuling secretion of insuling secretion of insulin are vell-known in the art and may be used or routinely modified to assess the ability of Polyperdies of the invention (including anthodies of the invention (including anthodies of the invention) to simulate insulin secretion. For example, insulin secretion is neasanted by PMAT assessing anti-art insulin anthodies; insulin secretion from parceatic better than the properties of the inventional by photose and also by certain noneitas/pendicks, and | highly proferred indication is discharged with the properties are limits. An additional ingle by preferred indication is a sometime as a sometime as a sometime as a sometime as a sometime and a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a sometime as a some |

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|                                                                                        | A highly preferred indication is diabetes reelling.  An additional lightly preferred indication is diabetes reelling.  An additional lightly preferred indication in diabetes (e.g., diabetic retinopathy diarse of second leadons associated with diabetes (e.g., diabetic retinopathy selective failures in repired as a described in the 'Renal Disabetes and disabetes and disabetes and disabete memopathy, nerve diseases and therve diamage (e.g., the to diabete memopathy, however, imported or expense and indicates and the work imported or expense and indicates, and indicates, heart disease, according to the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the |
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| J. 219: 547-551; Santerre et al. Proc.<br>Natl. Acad. Sci. USA 78: 4339-4343,<br>1981. | Assays for measuring secretion of massing to measuring secretion of may be used or routinely modified to the invention (melbuling analysis the ast and may be used or routinely modified to the invention (melbuling analysis of the invention (melbuling analysis of the invention (melbuling analysis of the invention) to simulate installin secretion for example, issuin secretion for measured by PMAT installin secretion from parceated by Bluose and also by certain proteins/poptides, and also by certain proteins/poptides, and also by certain proteins/poptides, and also by certain proteins/poptides, and also by certain proteins/poptides, and dishedes. Exemplery assays that may be used or routinely modified to test for simulation of melbuling antibodies and squaiss or from parceated cells by the invention) include assays disclosed in: Ahren, E. et al., (1999), E. M., et al., Erdostrinology, (1995), and, Mingalogy, 1997), K. m., et al., Erdostrinology, the contents of each of which is herein incorporated each of which is herein incorporated Parcearing to the standards.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                        | Simulation of insulin secretion from puncreate hea cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                        | 177                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                        | HUFCJ30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                        | 240                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| of the intrapy rate and skip, kerpal tunned syndrome and Daplaytern is contracture. An additional highly proferred indication is obesity and or complications associated with obesity. Additional highly proferred indications associated with obesity. Additional highly proferred indications include weight issue. Additional highly preferred indications are complications associated with insulin resistance.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | A highly preferred indication is adulabeds mellius. An additional highly preferred indication is a complication and inspire perferred indication is a complication associated with its action of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property of the property |
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| and or may be notinely generated. Exemplary pancreatic cells that may be used according to these assays include at INSI-tells are as semi-adherent cell line as a semi-adherent cell line as a semi-adherent cell line as a semi-adherent cell line as a semi-adherent cell line as a semi-adherent cell line from an X-ray induced from the area cells return characteristics typical of matric characteristics typical of matric planton and an area of the including glucose inducible insulin secretion.  Enderrones: Askini et al. Fractional planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a planton and a pla | caspass apoptosis a Nasys for<br>caspass apoptosis are well known in<br>that and may be used or notificly<br>modified to assess the shifting of<br>modified to assess the shifting of<br>modified in antibodies and agoniss or<br>antagonists of the invention) to<br>promote caspase protease-mediated<br>spoptosis. Apoptosis in gameratic<br>apoptosis. Apoptosis in gameratic<br>apoptosis. Apoptosis in gameratic<br>apoptosis. Apoptosis in gameratic<br>apoptosis. Apoptosis in gameratic<br>apoptosis, Apoptosis in gameratic<br>apoptosis and protease apoptosis that may<br>be used or routinely modified to test<br>processes on of diabetes. Exemplary<br>be used or routinely modified to test<br>possess good and apoptosis or<br>polypagnides of the invention include<br>the assays disclosed in: Loweth, Ac.<br>(1997); Sant, KS. et al., Bit Plantamed,<br>Mis Bin II, 3600; Canado II, Jantanes,<br>al. Liber Loweth, A., et al., Br Plantamed,<br>Indepted and apoptosis of all and apoptosis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| activate the PAS promoter element in described in the "Renal Disorders" are profession of PAS, a key croymer is creating the one programs. PAS promoters is creating the one of promoters in the programs are professional transcription of PAS, a key croymer. This should be seen and there demand inverses in As gene transcription is also increased in the creating and the professional transcription is also increased in the proposal professional inversion in the program of the professional professional inversional promoter of external activity (in physics), by physics of the professional professional inversional professional pro |
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| activate the FAS promoter element in arctivate the FAS promoter element in transcription of FAS, a key croyen for the pageness. FAS promoter is regulated by many transcription in horsens included more Than in increases FAS gove transcription is also samethal gluene more. This similation of transcription is also saverhal gluene dependent. Exemplary assays that may be used to rouninely more element activity (in the proposes) of the invention including autiloide so of the invention including autiloides of the invention including autiloides of the invention including autiloides of the invention including autiloides and against or antiloide to use for FAS proposes. The PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of the PAS of th |
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| 2/13 | HWADJ89 | 647 | Activation of          | Assays for the activation of            | A preferred embodiment of the          |
|------|---------|-----|------------------------|-----------------------------------------|----------------------------------------|
| £4   |         |     | serum response element | Response Element (SRE) are well-        | inhibiting (e.g., reducing) TNF alpha  |
|      |         |     | in immune cells (such  | known in the art and may be used or     | production. An alternative preferred   |
|      |         |     | as T-cells).           | routinely modified to assess the        | embodiment of the invention            |
|      |         |     |                        | ability of polypeptides of the          | includes a method for stimulating      |
|      |         |     |                        | invention (including antibodies and     | (c.g., increasing) TNF alpha           |
|      |         |     |                        | agonists or antagonists of the          | production. Preferred indications      |
|      |         |     |                        | invention) to regulate the serum        | include blood disorders (e.g., as      |
|      |         |     |                        | response factors and modulate the       | described below under "Immune          |
|      |         |     |                        | expression of genes involved in         | Activity", "Blood-Related              |
|      |         |     |                        | growth. Exemplary assays for            | Disorders", and/or "Cardiovascular     |
|      |         |     |                        | transcription through the SRE that      | Disorders"), Highly preferred          |
|      |         |     |                        | may be used or routinely modified to    | indications include autoimmune         |
|      |         |     |                        | test SRE activity of the polypeptides   | discases (e.g., rheumatoid arthritis,  |
|      |         |     |                        | of the invention (including antibodies  | systemic lupus erythematosis,          |
|      |         |     |                        | and agonists or antagonists of the      | Crohn"s disease, multiple sclerosis    |
|      |         |     |                        | invention) include assays disclosed in  | and/or as described below),            |
|      |         |     |                        | Berger et al., Gene 66:1-10 (1998);     | immunodeficiencies (e.g., as           |
|      |         |     |                        | Cullen and Malm, Methods in             | described below), boosting a T cell-   |
|      |         |     |                        | Enzymol 216:362-368 (1992);             | mediated immune response, and          |
|      |         |     |                        | Henthorn et al., Proc Natl Acad Sci     | suppressing a T cell-mediated          |
|      |         |     |                        | USA 85:6342-6346 (1988); and            | immune response. Additional highly     |
|      |         |     |                        | Black et al., Virus Genes 12(2):105-    | preferred indications include          |
|      |         |     |                        | 117 (1997), the content of each of      | inflammation and inflammatory          |
|      |         |     |                        | which are herein incorporated by        | disorders, and treating joint damage   |
|      |         |     |                        | reference in its entirety. T cells that | in patients with rheumatoid arthritis. |
|      |         |     |                        | may be used according to these          | An additional highly preferred         |
|      |         |     |                        | assays are publicly available (e.g.,    | indication is sepsis. Highly           |
|      |         |     |                        | through the ATCCTM). Exemplary          | preferred indications include          |
|      |         |     |                        | mouse T cells that may be used          | neoplastic diseases (e.g., leukemia,   |
|      |         |     |                        | according to these assays include the   | lymphoma, and/or as described          |
|      |         |     |                        | CTLL cell line, which is an IL-2        | below under "Hyperproliferative        |
|      |         |     |                        | dependent suspension culture of T       | Disorders"). Additionally, highly      |
|      |         |     |                        | cells with cytotoxic activity.          | preferred indications include          |
|      |         |     |                        |                                         | neoplasms and cancers, such as, for    |
|      |         |     |                        |                                         | evample, leuvenna, lymphoma,           |

| 243 | HWADJ89 | 647 | Simulation of insulin secretor from | Assays for measuring secretion of insulin are well-known in the art and                                                                                                                      | medenoum, glioma (e.g., malignant medenoum, glioma (e.g., malignant breat, lung, colon, sand prounce, and possine, breat, lung, colon, puncerali, brain, fiver and urmany cancer. Other preferred being on designation of the properties of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the proposition of the p |
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|     |         |     | pancreatic beta cells.              | may be used or routinely modified to<br>assess the ability of polypeptides of<br>the invention (including authodies<br>and agonists or antagonists of the<br>invention) to stimulate insulin | additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|     |         |     |                                     | secretion. For example, insulin                                                                                                                                                              | and/or other diseases and disorders as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| secretion is measured by FMAI  surge anti-red instill antibodies. Instill ascretion from parceatic bees closed and sold by execution from parceatic bees and distribution of instill accretion disheles. Exempliny seasoy that may be by certain proteins/peptides, and disheles. Exempliny seasoy that may be need or roundary medicited to test from parceatic cells) by polypeptides of the invention) include anaparises of the invention) include assays desloced in Antrol P., et al., An I Prisolo, T./Aft (P. P.) 1869-96. (1999); Li, M., et al., Endocranology. (1999); Li, M., et al., Endocranology. (1999); Li, M., et al., Endocranology. (1995), and, Minghin S. C., al., Andermology. (1995), and, Minghin S. C., al., Correction by the contents of each of which is herein incorporated by cardiality of these assays are publicly and or may be toution? generated. Examplary panceatic cells that may be used according to these assays we publicly and or may be toution? generated. Examplary panceatic cells that may be used according to these assays we publicly and or may be toution? generated. Examplary panceatic cells that may be used according to these assays we publicly and or may be toution? generated. Examplary panceatic cells that may be used according to these assays are publicly and or may be toution? generated. Examplary panceatic cells the may be used according to these assays are publicly and or may be contently generated. Examplary panceatic cells the contently generated. Examples of the contently generated. Examples of the contently generated. Examples of the contently of may be contently demander and X-ray induced ret transplantable induced and the stander of the contently of miner demander of the contently of miner demander of the contently of miner and an example cells in the contently demander demander of the contently demander and examples and the demander of the contently demander and examples and the demander of the contently demander and examples and the contently generated. | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage         | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease,  | stroke, impotence (e.g., due to     | diabetic neuropathy or blood vessel | blockage), seizures, mental           | confusion, drowsiness, nonketotic    | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis,             | microvascular disease, hypertension,  | stroke, and other diseases and          | disorders as described in the     | "Cardiovascular Disorders" section     | below), dyslipidemia, endocrine   | disorders (as described in the  | "Endocrine Disorders" section    | below), neuropathy, vision         | impairment (e.g., diabetic retinopathy | and blindness), ulcers and impaired  | wound healing, and infection (e.g., | infectious diseases and disorders as | described in the "Infectious           | Diseases" section below, especially  | of the urinary tract and skin), carpal | tunnel syndrome and Dupuytren's     | contracture). An additional       | highly preferred indication is obesity | and/or complications associated with | obesity. Additional highly preferred | indications include weight loss or  | alternatively, weight gain.    | Aditional highly preferred        | indications are complications   | associated with insulin resistance.  |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | secretion is measured by FMAT      | using anti-rat insulm antibodies.    | Insulin secretion from pancreatic beta | cells is upregulated by glucose and | also by certain proteins/peptides, and | disregulation is a key component in | diabetes. Exemplary assays that may | be used or routinely modified to test | for stimulation of insulin secretion | (from pancreatic cells) by       | polypeptides of the invention       | (including antibodies and agonists or | antagonists of the invention) include | assays disclosed in: Ahren, B., et al., | Am J Physiol, 277(4 Pt 2):R959-66 | (1999); Li, M., et al., Endocrinology, | 138(9):3735-40 (1997); Kim, K.H., | et al., FEBS Lett, 377(2):237-9 | (1995); and, Miraglia S et. al., | Journal of Biomolecular Screening, | 4:193-204 (1999), the contents of      | each of which is herein incorporated | by reference in its entirety.       | Pancreatic cells that may be used    | according to these assays are publicly | available (e.g., through the ATCCTM) | and/or may be routinely generated.     | Exemplary pancreatic cells that may | be used according to these assays | include rat INS-1 cells. INS-1 cells   | are a semi-adherent cell line        | established from cells isolated from | an X-ray induced rat transplantable | insulinoma. These cells retain | characteristics typical of native | pancreatic beta cells including | glucose inducible insulin secretion. |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 |                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |                                      |                                        |                                     |                                        |                                     |                                     |                                       |                                      |                                  |                                     |                                       |                                       |                                         |                                   |                                        |                                   |                                 |                                  |                                    |                                        |                                      |                                     |                                      |                                        |                                      |                                        |                                     |                                   |                                        |                                      |                                      |                                     |                                |                                   |                                 | _                                    |

|     |         |     |                   | References: Asfari et al.<br>Endocrinology 1992 130:167. |                                        |
|-----|---------|-----|-------------------|----------------------------------------------------------|----------------------------------------|
|     | HWBCP79 | 648 | Activation of     | Kinase assay. Kinase assays, for                         | A highly preferred embodiment          |
| 244 |         |     | Adipocyte ERK     | example an Elk-1 kinase assay, for                       | of the invention includes a method     |
|     |         |     | Signaling Pathway | ERK signal transduction that regulate                    | for stimulating adipocyte              |
|     |         |     |                   | cell proliferation or differentiation                    | proliferation. An alternative highly   |
|     |         |     |                   | are well known in the art and may be                     | preferred embodiment of the            |
|     |         |     |                   | used or routinely modified to assess                     | invention includes a method for        |
|     |         |     |                   | the ability of polypeptides of the                       | inhibiting adipocyte proliferation.    |
|     |         |     |                   | invention (including antibodies and                      | A highly preferred embodiment of       |
|     |         |     |                   | agonists or antagonists of the                           | the invention includes a method for    |
|     |         |     |                   | invention) to promote or inhibit cell                    | stimulating adipocyte differentiation. |
|     |         |     |                   | proliferation, activation, and                           | An alternative highly preferred        |
|     |         |     |                   | differentiation. Exemplary assays for                    | embodiment of the invention            |
|     |         |     |                   | ERK kinase activity that may be used                     | includes a method for inhibiting       |
|     |         |     |                   | or routinely modified to test ERK                        | adipocyte differentiation. A           |
|     |         |     |                   | kinase-induced activity of                               | highly preferred embodiment of the     |
|     |         |     |                   | polypeptides of the invention                            | invention includes a method for        |
|     |         |     |                   | (including antibodies and agonists or                    | stimulating (e.g., increasing)         |
|     |         |     |                   | antagonists of the invention) include                    | adipocyte activation. An alternative   |
|     |         |     |                   | the assays disclosed in Forrer et al.,                   | highly preferred embodiment of the     |
|     |         |     |                   | Biol Chem 379(8-9):1101-1110                             | invention includes a method for        |
|     |         |     |                   | (1998); Le Marchand-Brustel Y, Exp                       | inhibiting the activation of (e.g.,    |
|     |         |     |                   | Clin Endocrinol Diabetes                                 | decreasing) and/or inactivating        |
|     |         |     |                   | 107(2):126-132 (1999); Kyriakis JM,                      | adipocytes. Highly preferred           |
|     |         |     |                   | Biochem Soc Symp 64:29-48 (1999);                        | indications include endocrine          |
|     |         |     |                   | Chang and Karin, Nature                                  | disorders (e.g., as described below    |
|     |         |     |                   | 410(6824):37-40 (2001); and Cobb                         | under "Endocrine Disorders").          |
|     |         |     |                   | MH, Prog Biophys Mol Biol 71(3-                          | Highly preferred indications also      |
|     |         |     |                   | 4):479-500 (1999); the contents of                       | include neoplastic diseases (e.g.,     |
|     |         |     |                   | each of which are herein                                 | lipomas, liposarcomas, and/or as       |
|     |         |     |                   | incorporated by reference in its                         | described below under                  |
|     |         |     |                   | entirety. Mouse adipocyte cells that                     | "Hyperproliferative Disorders").       |
|     |         |     |                   | may be used according to these                           | Preferred indications include blood    |
|     |         |     |                   | assays are publicly available (e.g.,                     | disorders (e.g., hypertension,         |
|     |         |     |                   | through the ATCCTM). Exemplary                           | congestive heart failure, blood vessel |
|     |         |     |                   | mouse adipocyte cells that may be                        | blockage, heart disease, stroke,       |

| inched 713-Li cells 713-Li sen inched 713-Li cells 713-Li sen adherent mouse predipocyte cell line that is continuous substanti of 313 filtrobiast cells developed through todain slashton and undergo a pre-dipocyte to adipose-like a row-weston under appropriate differentiation conditions known in the art. | ys impotence and/or as described below L1 is an under "Immune Activity", Cardiovascular Dislochers", and/or |                                                              | ike disorders (e.g., as described below nder "Neural Activity and | nown in Neurological Discases"), and infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is<br>diabetes mellitus. An additional | highly preferred indication is a | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | (e a due to dishetic neuronathy) | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | hyperglycemic-hyperosmolar coma. | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other discases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine<br>disorders (as described in the |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------|----------------------------------------------------------------------|----------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|-------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                   | used according to these assimplied of 313-L1 cells. 313-adherent mouse preadipoor                           | 3T3 fibroblast cells develor<br>through clonal isolation and | a pre-adipocyte to adipose-l<br>conversion under appropria        | differentiation conditions k                                             | m ar                         |                                                                      |                                  |                                       |                                      |                                   |                                        |                                    |                                      |                                  |                                       |                                 |                                     |                             |                                  |                                     |                           |                                      |                                |                               |                                    |                                                                   |
|                                                                                                                                                                                                                                                                                                                   |                                                                                                             |                                                              |                                                                   |                                                                          |                              |                                                                      |                                  |                                       |                                      |                                   |                                        |                                    |                                      |                                  |                                       |                                 |                                     |                             |                                  |                                     |                           |                                      |                                |                               |                                    |                                                                   |

|  | "Endo       | "Endocrine Disordere" section           |
|--|-------------|-----------------------------------------|
|  | 1-1-1       | CHIECASON CONTROL                       |
|  | Delow       | betow), neuropamy, vision               |
|  | and bi      | and blindness) alcers and impaired      |
|  | omow        | wound healing, infection (e.g.,         |
|  | infecti     | infectious diseases and disorders as    |
|  | descri      | described in the "Infectious            |
|  | Diseas      | Diseases" section below (particularly   |
|  | of the      | of the urinary tract and skin). An      |
|  | additio     | additional highly preferred indication  |
|  | is obes     | is obesity and/or complications         |
|  | associ      | associated with obesity. Additional     |
|  | highly      | highly preferred indications include    |
|  | weigh       | weight loss or alternatively, weight    |
|  | gain.       | Additional highly                       |
|  | brefer      | preferred indications are               |
|  | compl       | complications associated with insulin   |
|  | resistance. | nce. Additional highly                  |
|  | l prefer    | preferred indications are disorders of  |
|  | the m       | the musculoskeletal systems             |
|  | includ      | including myopathies, muscular          |
|  | dystro      | dystrophy, and/or as described          |
|  | herein.     | . Additional highly                     |
|  | prefer      | preferred indications include,          |
|  | hypert      | hypertension, coronary artery           |
|  | diseas      | disease, dyslipidemia, gallstones,      |
|  | osteoa      | osteoarthritis, degenerative arthritis, |
|  | eating      | eating disorders, fibrosis, cachexia,   |
|  | and ki      | and kidney diseases or disorders.       |
|  | Prefer      | Preferred indications include           |
|  | leopla      | neoplasms and cancer, such as,          |
|  | Iymph       | lymphoma, leukemia and breast,          |
|  | colon,      | colon, and kidney cancer. Additional    |
|  | brefer      | preferred indications include           |
|  | melan       | melanoma, prostate, lung,               |
|  | pancre      | pancreatic, esophageal, stomach,        |
|  | brain,      | brain, liver, and urinary cancer.       |

| Highly preferred indications include lipomas and liposacromas. Other preferred indications include benign dyspoilferaitve disorders and preneplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dyspalsia. | allegy preferred indications include allegy and salam. Additional highly preferred indications include insume and hierarcopicited disorders (e.g., as Gescriech below under Trammer and hierarcopicited disorders (e.g., as described below under Trammer Activity, and "Blood-Raland Disorders"), autoimmund earlinis, systemic lipus cryderandosis, asystemic lipus cryderandosis, systemic lipus cryderandosis, asystemic lipus cryderandosis, and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consideration and consid |
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|                                                                                                                                                                                                                                   | activation of Ta-cilis are well known in the art and may be used or muturity modified to assess the ability of polyspetides of the ability of polyspetides of the ability of polyspetides of the ability of polyspetides of the ability of polyspetides of the activation of sultrained or inhibit production of Ta-cilis. Exemplary assays that may be used or routinely modified or Ta-cilis. Exemplary assays that may be used or routinely modified on may be used or routinely modified on may be used or routinely modified and antibodies of the invention floation for the invention of the activation in modified, for example, assays such as disclosed and or cited in: Robinson, production and or cited in: Robinson, discussed the Med Bull; Se (4) 296–208 (2000), and colon, et al., Telebra type 2 cell-directed therapy floatine and with the antibory Exemplary cells that may be used according to these there micropyroated by reference in may be used according to these are to a second of which are may be used according to these are to a second of which are may be used according to these contents of each of which are may be used according to these contents of each of which are may be used according to these contents of each of which are level in comported by reference in the second of the cited in Life according to these contents of each of which are level in a compared from the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the colon and the cited in the cited in the colon and the cited in the colon and the cited in the cited in the cited in the cited in cited in the cited in the c |
|                                                                                                                                                                                                                                   | Production of T-eelbs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                   | 8.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                   | HWBCP79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                   | 244                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| measured as a marker of Th2 cell area defavor. The Colls are a class of Teells that secrete Li4, IL10, IL11, and Li6, Fasters that indicate differentiation and activation of the differentiation and activation of Th2 cells play a major roble in the initiation and pathogenesis of altery and salmar. Primary I helper 2 and salmar, The play 2 and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary and salmary an | transcription of Maile Enzyme are weak-loow in the art and may be used or routinely modified to assess the ability of polypsyrides of the invention (including antibodies of the invention) to regulate transcription of Malic Incyme at they outsome a layer outsome a layer outsome a layer of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the antibodies of the invention (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and invention) (including antibodies and including antibodies and includ |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 059                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HWBFX31                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|     |         |     |                       | in: Streeper, R.S., et al., Mol       | disorders (as described in the         |
|-----|---------|-----|-----------------------|---------------------------------------|----------------------------------------|
|     |         |     |                       | Endocrinol, 12(11):1778-91 (1998);    | "Endocrine Disorders" section          |
|     |         |     |                       | Garcia-Jimenez, C., et al., Mol       | below), neuropathy, vision             |
|     |         |     |                       | Endocrinol, 8(10):1361-9 (1994);      | impairment (e.g., diabetic retinopathy |
|     |         |     |                       | Barroso, I., et al., J Biol Chem,     | and blindness), ulcers and impaired    |
|     |         |     |                       | 274(25):17997-8004 (1999);            | wound healing, and infection (e.g.,    |
|     |         |     |                       | Ijpenberg, A., et al., J Biol Chem,   | infectious diseases and disorders as   |
|     |         |     |                       | 272(32):20108-20117 (1997);           | described in the "Infectious           |
|     |         |     |                       | Berger, et al., Gene 66:1-10 (1988);  | Diseases" section below, especially    |
|     |         |     |                       | and, Cullen, B., et al., Methods in   | of the urinary tract and skin), carpal |
|     |         |     |                       | Enzymol. 216:362-368 (1992), the      | tunnel syndrome and Dupuytren's        |
|     |         |     |                       | contents of each of which is herein   | contracture). An additional            |
|     |         |     |                       | incorporated by reference in its      | highly preferred indication is obesity |
|     |         |     |                       | entirety. Hepatocytes that may be     | and/or complications associated with   |
|     |         |     |                       | used according to these assays are    | obesity. Additional highly preferred   |
|     |         |     |                       | publicly available (e.g., through the | indications include weight loss or     |
|     |         |     |                       | ATCCTM) and/or may be routinely       | alternatively, weight gain.            |
|     |         |     |                       | generated. Exemplary hepatocytes      | Aditional highly preferred             |
|     |         |     |                       | that may be used according to these   | indications are complications          |
|     |         |     |                       | assays includes the H4IIE rat liver   | associated with insulin resistance.    |
|     |         |     |                       | hepatoma cell line.                   |                                        |
|     | HWHGZ51 | 651 | Activation of         | Assays for the activation of          | Highly preferred indications           |
| 247 |         |     | transcription through | transcription through the Gamma       | include neoplastic diseases (e.g.,     |
|     |         |     | GAS response element  | Interferon Activation Site (GAS)      | leukemia, lymphoma, and/or as          |
|     |         |     | in immune cells (such | response element are well-known in    | described below under                  |
|     |         |     | as T-cells).          | the art and may be used or routinely  | "Hyperproliferative Disorders").       |
|     |         |     |                       | modified to assess the ability of     | Highly preferred indications include   |
|     |         |     |                       | polypeptides of the invention         | neoplasms and cancers, such as, for    |
|     |         |     |                       | (including antibodies and agonists or | example, leukemia, lymphoma (e.g.,     |
|     |         |     |                       | antagonists of the invention) to      | T cell lymphoma, Burkitt's             |
|     |         |     |                       | regulate STAT transcription factors   | lymphoma, non-Hodgkins                 |
|     |         |     |                       | and modulate gene expression          | lymphoma, Hodgkin"s disease),          |
|     |         |     |                       | involved in a wide variety of cell    | melanoma, and prostate, breast, lung,  |
|     |         |     |                       | functions. Exemplary assays for       | colon, pancreatic, esophageal,         |
|     |         |     |                       | transcription through the GAS         | stomach, brain, liver and urinary      |
|     |         |     |                       | response element that may be used or  | cancer. Other preferred indications    |
|     |         |     |                       | routinely modified to test GAS-       | include benign dysproliferative        |

| polypeptides of the invention including authorities of the invention including authorities and agoustist or including authorities and agoustist or amagonists of the invention) include assays disclosed in Berger et al., Graw 66:1;10;10;93;1, Cultien and Mahn, Methods in Eazymol 21;65;62;86;1,993;1, Farliam et al., 16;62;84;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,993;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190;1,190; | polyperidies of the inventor and applies of the inventor) indiantial anniholdes and agoing anniholdes and agoing anniholdes and agoing anniholdes and agoing diaglosed in Berger et al. Gene 66-11 (10 1998); Cullen and Malin, Methods in Enzymol Malin, Methods in Enzymol Proc Natl Acad Sci 1828 85:643-187 (1992); Henthorn et al. Blood 34(6); 1980-199 (1099); the contents of each of with an web to impropriate the contents of each of which are been impropriately. Exemplar points of each of which are been impropriately as a supplied by a variable for generated by telescence in the formatty in beard according to the assistance of the formatty on beard according to the assistance of the formatty of the each according to the assistance of the formatty of the each according to the assistance of the formatty of the each according to the assistance of the formatty of the each according to the assistance of the formatty include for CTL to line, which is a suspension of thin. 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Preterred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple selerosis |                                                                                   | inflammation and inflammatory disorders.  Highly preferred indications include blood disorders (e.g., as described below under Timmure Activity", "Blood-Related Disorders", and/or "Cardiovascular" in Disorders", and/or "Cardiovascular" in Disorders", and/or "Cardiovascular" in Disorders", and inferience of virtual prisorders", and or inferience of virtual prisorders". | 9                                                                                                      | disease, inflammatory bowel disease,<br>sensis neutronenia neutronhilia |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | response element activity of polypeptides of the invention (including antibodies and agonist of the invention) and activities of the invention in the polypeptides. | antagonists of the invention) incl<br>assays disclosed in Berger et al.,<br>Gene 66:1-10 (1998), Cullen and<br>Malmi, Methods in Enzymol       | 2 to 20-20-20-20<br>To 20-20-20-20<br>To 20-20-20-20-20-20-20-20-20-20-20-20-20-2 | incorporated by reference in its<br>craticey. Exemplary mouser Teed<br>that may be used according to the<br>usesy, are publicly available (e.g.<br>from publicly available (e.g.<br>from the ATCCPA). Exempla<br>cells that may be used according                                                                                                                                  | Those assists madue for LTL. or line, which is a supersion outline.  TL-2 dependent cytoroxic T cells. |                                                                         |

| psoriasis, suppression of immune<br>reactions to transplanted organs and<br>tissues, hornophilia,<br>hypercoagulation, disbetes mellitus,<br>endocardisi, meningtis, Lyme<br>Disease, and saftma and allergy. | 2 WELLER ELER PARENCE SERVICE ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL ELER CONTROL E |
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|                                                                                                                                                                                                               | Production of MCP-1 MCP-1 PAMTA Assussy for a minimum conduction to you for a first produced by a large variety of stells and activation of monocycles and Testils are well known in the art and may be used or roundly modified to assess the ability of hypophases of the mineration of monocycles and Testils agonts so a managenists of the mineration) to mediane immune ordering assays that set for immune clean extension of mediane clean activation of monocycle activation, induced elementaris, and modulate immune clean activation of cell articles are for immune orderidation, induced elementaris, and modulate immune orderidation of monocycle activation of cell articles and the striction of monocycle activation of cell articles and effect of the invention of monocycle activition of monocycle and immune orderidation activity of polypophices of the invention (including ambides and agent at 1132—1134 Biomochain Screening 21132—1134 Biomochain Screening 21134—1134 Biomochain Screening 21134—1134 Biomochain Screening 21134—1134 Biomochain Screening 21134—1134 Biomochain Screening 21134 Biomochain Screening 2 |
|                                                                                                                                                                                                               | HWIIGZ51 651                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                               | 247                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|     |         |     |                       | Satthapom and Eremin, J R Coll                                 | arthritis, AIDS, granulomatous          |
|-----|---------|-----|-----------------------|----------------------------------------------------------------|-----------------------------------------|
|     |         |     |                       | Surg Ednb 45(1):9-19 (2001); and<br>Verbasselt of al Therminol | disease, inflammatory bowel disease,    |
|     |         |     |                       | 158:2919-2925 (1997), the contents                             | psoriasis, suppression of immune        |
|     |         |     |                       | of each of which are herein                                    | reactions to transplanted organs and    |
|     |         |     |                       | incorporated by reference in its                               | tissues, hemophilia,                    |
|     |         |     |                       | entirety. Human dendritic cells that                           | hypercoagulation, diabetes mellitus,    |
|     |         |     |                       | may be used according to these                                 | endocarditis, meningitis (bacterial     |
|     |         |     |                       | assays may be isolated using                                   | and viral), Lyme Discase, asthma,       |
|     |         |     |                       | techniques disclosed herein or                                 | and allergy Preferred indications       |
|     |         |     |                       | otherwise known in the art. Human                              | also include neoplastic diseases (e.g., |
|     |         |     |                       | dendritic cells are antigen presenting                         | leukemia, lymphoma, and/or as           |
|     |         |     |                       | cells in suspension culture, which,                            | described below under                   |
|     |         |     |                       | when activated by antigen and/or                               | "Hyperproliferative Disorders").        |
|     |         |     |                       | cytokines, initiate and upregulate T                           | Highly preferred indications include    |
|     |         |     |                       | cell proliferation and functional                              | neoplasms and cancers, such as,         |
|     |         |     |                       | activities.                                                    | leukemia, lymphoma, prostate,           |
|     |         |     |                       |                                                                | breast, lung, colon, pancreatic,        |
|     |         |     |                       |                                                                | esophageal, stomach, brain, liver,      |
|     |         |     |                       |                                                                | and urinary cancer. Other preferred     |
|     |         |     |                       |                                                                | indications include benign              |
|     |         |     |                       |                                                                | dysproliferative disorders and pre-     |
|     |         |     |                       |                                                                | neoplastic conditions, such as, for     |
|     |         |     |                       |                                                                | example, hyperplasia, metaplasia,       |
|     |         |     |                       |                                                                | and/or dysplasia.                       |
|     | HWHGZ51 | 651 | Activation of         | Assays for the activation of                                   | Highly preferred indications include    |
| 247 |         |     | transcription through | transcription through the NFKB                                 | asthma, allergy, hypersensitivity       |
|     |         |     | NFKB response         | response element are well-known in                             | reactions, and inflammation.            |
|     |         |     | element in immune     | the art and may be used or routinely                           | Preferred indications include           |
|     |         |     | cells (such as EOL1   | modified to assess the ability of                              | infection (e.g., an infectious disease  |
|     |         |     | cells).               | polypeptides of the invention                                  | as described below under "Infectious    |
|     |         |     |                       | (including antibodies and agonists or                          | Disease"), immunological disorders,     |
|     |         |     |                       | antagonists of the invention) to                               | inflammation and inflammatory           |
|     |         |     |                       | regulate NFKB transcription factors                            | disorders (e.g., as described below     |
|     |         |     |                       | and modulate expression of                                     | under "Immune Activity", and            |
|     |         |     |                       | immunomodulatory genes.                                        | "Blood-Related Disorders").             |
|     |         |     |                       | Exemplary assays for transcription                             | Preferred indications include           |

| _                                 | _                                    | _                                 | _                                   | _                                   | _                                  | _                                      | _                                   | _                           | _                           | _                                   | _                              | _                          | _                                  | _                                    | _                                | _                                     | _                                    | _                               | _                              | _                                    | _                                 | _                              | _                                     | _                                 | _                                 | _                            | _                             | _                                 | _                                  | _                           | _                                | _                              | _                                | _                                   | _                               | _                          |
|-----------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|------------------------------------|----------------------------------------|-------------------------------------|-----------------------------|-----------------------------|-------------------------------------|--------------------------------|----------------------------|------------------------------------|--------------------------------------|----------------------------------|---------------------------------------|--------------------------------------|---------------------------------|--------------------------------|--------------------------------------|-----------------------------------|--------------------------------|---------------------------------------|-----------------------------------|-----------------------------------|------------------------------|-------------------------------|-----------------------------------|------------------------------------|-----------------------------|----------------------------------|--------------------------------|----------------------------------|-------------------------------------|---------------------------------|----------------------------|
| autoimmune diseases (e.g.,        | rheumatoid arthritis, systemic lupus | erythematosis, multiple sclerosis | and/or as described below) and      | immunodeficiencies (e.g., as        | described below).                  |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |                              |                               |                                   |                                    |                             |                                  |                                |                                  |                                     |                                 |                            |
| through the NFKB response element | that may be used or rountinely       | modified to test NFKB-response    | element activity of polypeptides of | the invention (including antibodies | and agonists or antagonists of the | invention) include assays disclosed in | Berger et al., Gene 66:1-10 (1998); | Cullen and Malm, Methods in | Enzymol 216:362-368 (1992); | Henthorn et al., Proc Natl Acad Sci | USA 85:6342-6346 (1988); Valle | Blazquez et al, Immunology | 90(3):455-460 (1997); Aramburau et | al., J Exp Med 82(3):801-810 (1995); | and Frascr et al., 29(3):838-844 | (1999), the contents of each of which | are herein incorporated by reference | in its entirety. For example, a | reporter assay (which measures | increases in transcription inducible | from a NFkB responsive element in | EOL-1 cells) may link the NFKB | element to a repeorter gene and binds | to the NFKB transcription factor, | which is upregulated by cytokines | and other factors. Exemplary | immune cells that may be used | according to these assays include | eosinophils such as the human EOL- | 1 cell line of eosinophils. | Eosinophils are a type of immune | cell important in the allergic | responses; they are recruited to | tissues and mediate the inflammtory | response of late stage allergic | reaction. Eol-1 is a human |
|                                   |                                      |                                   |                                     |                                     |                                    |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |                              |                               |                                   |                                    |                             |                                  |                                |                                  |                                     |                                 |                            |
|                                   |                                      |                                   |                                     |                                     |                                    |                                        |                                     |                             |                             |                                     |                                |                            |                                    |                                      |                                  |                                       |                                      |                                 |                                |                                      |                                   |                                |                                       |                                   |                                   |                              |                               |                                   |                                    |                             |                                  |                                |                                  |                                     |                                 |                            |

|   | Adinocyte ERK     | Kinase assay. Kinase assays, for<br>example an Elk-1 kinase assay for       | A highly preferred embodiment<br>of the invention includes a method    |
|---|-------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------|
|   | Signaling Pathway | ERK signal transduction that regulate cell proliferation or differentiation | for stimulating adipocyte proliferation. An alternative highly         |
|   |                   | are well known in the art and may be                                        | preferred embodiment of the                                            |
|   |                   | used or routinely modified to assess<br>the ability of polymentides of the  | invention includes a method for<br>inhibiting adinocyte proliferation. |
|   |                   | invention (including antibodies and                                         | A highly preferred embodiment of                                       |
| _ |                   | agonists or antagonists of the                                              | the invention includes a method for                                    |
|   |                   | invention) to promote or inhibit cell                                       | stimulating adipocyte differentiation.                                 |
|   |                   | proliferation, activation, and                                              | An alternative highly preferred                                        |
|   |                   | differentiation. Exemplary assays for                                       | embodiment of the invention                                            |
|   |                   | ERK kinase activity that may be used                                        | includes a method for inhibiting                                       |
|   |                   | Of fourthein modified to test EAN                                           | highly amplemed ambodinger of the                                      |
|   |                   | nolynentides of the invention                                               | invention includes a method for                                        |
|   |                   | (including antibodies and agonists or                                       | stimulating (e.g., increasing)                                         |
|   |                   | antagonists of the invention) include                                       | adipocyte activation. An alternative                                   |
|   |                   | the assays disclosed in Forrer et al.,                                      | highly preferred embodiment of the                                     |
|   |                   | Biol Chem 379(8-9):1101-1110                                                | invention includes a method for                                        |
|   |                   | (1998); Le Marchand-Brustel Y, Exp                                          | inhibiting the activation of (e.g.,                                    |
|   |                   | Clin Endocrinol Diabetes                                                    | decreasing) and/or inactivating                                        |
|   |                   | 107(2):126-132 (1999); Kyriakis JM,                                         | adipocytes. Highly preferred                                           |
|   |                   | Biochem Soc Symp 64:29-48 (1999);                                           | indications include endocrine                                          |
|   |                   | Chang and Karin, Nature                                                     | disorders (e.g., as described below                                    |
|   |                   | 410(6824):37-40 (2001); and Cobb                                            | under "Endocrine Disorders").                                          |
|   |                   | MH, Prog Biophys Mol Biol 71(3-                                             | Highly preferred indications also                                      |
|   |                   | 4):479-500 (1999); the contents of                                          | include neoplastic diseases (e.g.,                                     |
|   |                   | each of which are herein                                                    | lipomas, liposarcomas, and/or as                                       |
|   |                   | incorporated by reference in its                                            | described below under                                                  |
|   |                   | entirety. Mouse adipocyte cells that                                        | "Hyperproliferative Disorders").                                       |
|   |                   | may be used according to these                                              | Preferred indications include blood                                    |
|   |                   | assays are publicly available (e.g.,                                        | disorders (e.g., hypertension,                                         |
|   |                   | through the ATCCTM). Exemplary                                              | congestive heart failure, blood vessel                                 |
|   |                   | mouse adipocyte cells that may be                                           | blockage, heart disease, stroke,                                       |

| under "Immune Activity",<br>"Cardiovascular Disorders", and/or      | "Blood-Related Disorders"), immune     | disorders (e.g., as described below | disorder "Immune Activity"), neural  | under "Neural Activity and      | Neurological Diseases"), and        | infection (e.g., as described below | under "Infectious Disease"). | A highly preferred indication is | diabetes mellitus. An additional | highly preferred indication is a | complication associated with | diabetes (e.g., diabetic retinopathy, | diabetic nephropathy, kidney disease | (e.g., renal failure, nephropathy | and/or other diseases and disorders as | described in the "Renal Disorders" | section below), diabetic neuropathy, | nerve disease and nerve damage | (e.g., due to diabetic neuropathy), | blood vessel blockage, heart disease, | stroke, impotence (e.g., due to | diabetic neuropathy or blood vessel | blockage), seizures, mental | confusion, drowsiness, nonketotic | hyperglycemic-hyperosmolar coma, | cardiovascular disease (e.g., heart | disease, atherosclerosis, | microvascular disease, hypertension, | stroke, and other diseases and | disorders as described in the | "Cardiovascular Disorders" section | below), dyslipidemia, endocrine | disorders (as described in the | "Endocrine Disorders" section |
|---------------------------------------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|---------------------------------|-------------------------------------|-------------------------------------|------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------|---------------------------------------|--------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------|-------------------------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------|-----------------------------------|----------------------------------|-------------------------------------|---------------------------|--------------------------------------|--------------------------------|-------------------------------|------------------------------------|---------------------------------|--------------------------------|-------------------------------|
| include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell | line that is a continuous substrain of | 313 fibroblast cells developed      | through clonal isolation and undergo | a pre-adipocyte to adipose-like | differentiation conditions known in | the art.                            |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |
|                                                                     |                                        |                                     |                                      |                                 |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |
|                                                                     |                                        |                                     |                                      |                                 |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                |                               |
|                                                                     |                                        |                                     |                                      |                                 |                                     |                                     |                              |                                  |                                  |                                  |                              |                                       |                                      |                                   |                                        |                                    |                                      |                                |                                     |                                       |                                 |                                     |                             |                                   |                                  |                                     |                           |                                      |                                |                               |                                    |                                 |                                | _                             |

|   | below), 1   | below), neuropathy, vision                                                |
|---|-------------|---------------------------------------------------------------------------|
|   | and blind   | and blindness), ulcers and impaired                                       |
|   | wound he    | wound healing, infection (e.g.,<br>infectious diseases and disorders as   |
|   | described   | described in the "Infectious                                              |
|   | Diseases    | Diseases" section below (particularly                                     |
|   | of the uri  | of the urinary tract and skin). An                                        |
|   | additiona   | additional highly preferred indication<br>is obseity and/or complications |
|   | associate   | associated with obesity. Additional                                       |
|   | nighly pr   | highly preferred indications include                                      |
|   | weight lo   | weight loss or alternatively, weight                                      |
|   | gain.       | Additional highly                                                         |
|   | preferred   | preferred indications are                                                 |
|   | complica    | as as                                                                     |
|   | resistance. | <ol> <li>Additional highly</li> </ol>                                     |
|   | preferred   | preferred indications are disorders of                                    |
|   | the musc    | the musculoskeletal systems                                               |
|   | including   | including myopathies, muscular                                            |
|   | dystrophy   | ŝ                                                                         |
|   | herein.     | Additional highly                                                         |
|   | preferred   | preferred indications include,                                            |
|   | hypertens   | hypertension, coronary artery                                             |
|   | disease, d  | disease, dyslipidemia, gallstones,                                        |
|   | osteoarth   | osteoarthritis, degenerative arthritis,                                   |
|   | eating dis  | eating disorders, fibrosis, cachexia,                                     |
|   | and kidne   | and kidney diseases or disorders.                                         |
|   | Preferred   | Preferred indications include                                             |
|   | neoplasm    | neoplasms and cancer, such as,                                            |
|   | Iymphom     | lymphoma, leukemia and breast,                                            |
|   | colon, an   | colon, and kidney cancer. Additional                                      |
|   | preferred   | preferred indications include                                             |
|   | melanom     | melanoma, prostate, lung,                                                 |
|   | pancreati   | pancreatic, esophageal, stomach,                                          |
|   | brain, liv  | brain, liver, and urinary cancer.                                         |
| _ | I Highly D  | Highly preferred indications include                                      |

|     |         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and prenoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|---------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------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| 248 | HWTBK81 | 653 | transcription through through through through through through the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the description of the desc | transarrigion through the NFBB transarrigion through the NFBB transarrigion through the NFBB transarrigion through the NFBB transarrigion through the NFBB transarrigion to week-leavann in the art and may be used or toutiebly modified to snews the shift of mention of including unthodics and agonists or regulate NFBB transarrigion factors and agonists or regulate NFBB transarrigion factors immunomodulatory genes. See the NFB transarrigion for the standards of the standards of transarrigion from the standards of the standards of the standards of the standards of the standards of the standards of the standards of the invention (including anthodies of the invention include usany of sickle (1988); Collifer and Main, Methods in invention include usany of sickle (1988). Cellifer and Main, Methods in invention include usany of sickle (1988); Henthom et al., Proc Mail And Sci (1993); Cambumon of Sci (1993); Atambumon et al., The Med Sci (1983) and al., The Med Sci (1983) and a standards of each of which the standard by reference their in socionard by reference in its series. To cells that may be | inflammation and inflammatory include inflammatory and inflammatory advances. Highly preferred inflammatory referred indexions include inflammatory preferred indexions include immunological and perantopostic disorders (e.g., see section between word "mmune Activity", "Biock-Catado Cardiovascular Disorders", andro for Cardiovascular Disorders", inflato preferred and autoimmune diseases (e.g., rheumatoid adriftis, segment lupra evidentions include autoimmune diseases (e.g., rheumatoid adriftis, segment lupra evidentions). Inflato preferred andications include evidencial pulphosis diseases (e.g., rheumatoid adriftis, sea described below), and immunedeficiencies (e.g., as described below), and immunedeficiencies in sincition (e.g., ALIS, andro am indication include neophastic diseases (e.g., reflamona, under "Infections Essens"). Highly preferred indications include neophastic diseases (e.g., reflamona, under estered indications include neophastica diseases (e.g., reflamona, under estered indications include neophastica algorian, and prostac, heart, improprientian, and prostac, heart, lung, coltor, panerestic, bring, coltor, panerestic, bring, regulared, algorian, bring in letter neophastical, algorian, and prostac, heart, lung, coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, present, lung, coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, preferred panerestic, bring coltor, panerestic, preferred panerestic, bring coltor, panerestic, bring coltor, panerestic, bring coltor, panerestic, pane |

| dispensions include benign dispensions include benign morphasic conditions, such as for morphasic conditions, such as for morphasic conditions, such as for morphasic conditions, such as for morphic physical fredered and or dop-plasin. Fredered purely openial, lethopenia, puncytopenial, lethopenia, lethopenia, puncytopenial, lethopenia, arthrifis, ADS, granulomatous disease, influentamight is, tyme arthrifis, ADS, granulomatous activities, and propression of immune processing lethopenial diseases, suppression of immune Diseases, suppression of immune presents or transplanted organs, astimus and allery. | A highly preferred embediance<br>of the investion includes a method<br>for seimulating the production of<br>GOM-GSF. An attenumive highly<br>preferred embediance to the<br>minhising the production of GOM-<br>CSF. Highly preferred indications<br>include inflammation and<br>inflammatously discovers. An additional lightly preferred indication<br>additional lightly preferred indication<br>in inflation and lightly preferred indication<br>with a discoverse of a describe below<br>under "Infectious Disease". In<br>Highly preferred indications include<br>blood discoverse (e.g., nettropenia<br>control of the production of neutropenia<br>for the previous of the preferred indications include<br>blood discoverse (e.g., nettropenia |
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| publicly available (e.g., through or horizon are coording to these assays are ATCT'N). Teals that may be used available (e.g., through the available (e.g., through the ATCT'N). Exampled human Teells that may be used according to these ways include the LHRKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Claw-GSF PMCT (DM-CSF) is<br>crow-GSF pMCT (DM-CSF) is<br>crow-GSF waith and Totals,<br>more objects of the companies of<br>flowly and proliferation of<br>flowly and proliferation of<br>flowly and proliferation of<br>progenitors and enhances<br>progenitors and enhances<br>progenitors and enhances<br>progenitors and enhances<br>progenitors and enhances<br>progenitors and encorphage,<br>monocytes and macrophage,<br>monocytes and macrophage in<br>important role in the differentiation<br>in protent role in the differentiation<br>increases antigen presentation. GM-<br>for is considered to be a<br>profil mannancy cytokire. Assays<br>for intermediatory proteins that<br>profil mannancy cytokire. Assays                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Production of GM-CSF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 653                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HAGAI8S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 249                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

|                                      |                                      |                                    |                                     |                                     |                                       |                                   | Ţ                                      | ,:                                   |                                    |                                       |                                    |                                     |                                       |                                   |                                 | _                                     |                                       |                                     |                                      |                                      |                                     | g                                   |                                    |                                   | H                                      | _                                       |                                     |                                      |                                   | _                                   |                                       |                                     | ×                                     |                                   |                                  |
|--------------------------------------|--------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|------------------------------------|---------------------------------------|------------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|---------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-----------------------------------|----------------------------------------|-----------------------------------------|-------------------------------------|--------------------------------------|-----------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|-----------------------------------|----------------------------------|
| and/or as described below under      | "Immune Activity", "Blood-Related    | Disorders", and/or "Cardiovascular | Disorders"). Highly preferred       | indications also include autoimmune | diseases (e.g., rheumatoid arthritis, | systemic lupus erythematosis,     | multiple sclerosis and/or as described | below) and immunodeficiencies (e.g., | as described below). Additional    | highly preferred indications include  | asthma. Highly preferred           | indications include neoplastic      | diseases (e.g., leukemia (e.g., acute | lymphoblastic leukemia, and acute | myelogenous leukemia), lymphoma | (c.g., non-Hodgkin"s lymphoma and     | Hodgkin"s disease), and/or as         | described below under               | "Hyperproliferative Disorders").     | Highly preferred indications include | neoplasms and cancers, such as,     | leukemia, lymphoma, melanoma, and   | prostate, breast, lung, colon,     | pancreatic, esophageal, stomach,  | brain, liver and urinary cancer. Other | preferred indications include benign    | dysproliferative disorders and pre- | neoplastic conditions, such as, for  | example, hyperplasia, metaplasia, | and/or dysplasia. Highly preferred  | indications include: suppression of   | immune reactions to transplanted    | organs and tissues (e.g., bone marrow | transplant); accelerating myeloid | recovery; and mobilizing         |
| are well known in the art and may be | used or routinely modified to assess | the ability of polypeptides of the | invention (including antibodies and | agonists or antagonists of the      | invention) to mediate                 | immunomodulation and modulate the | growth and differentiation of          | leukocytes. Exemplary assays that    | test for immunomodulatory proteins | evaluate the production of cytokines, | such as GM-CSF, and the activation | of T cells. Such assays that may be | used or routinely modified to test    | immunomodulatory activity of      | polypeptides of the invention   | (including antibodies and agonists or | antagonists of the invention) include | the assays disclosed in Miraglia et | al., J Biomolecular Screening 4:193- | 204 (1999); Rowland et al.,          | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000); and Ye et | al., J Leukoc Biol (58(2):225-233, | the contents of each of which are | herein incorporated by reference in    | its entirety. Natural killer cells that | may be used according to these      | assays are publicly available (e.g., | through the ATCCTM) or may be     | isolated using techniques disclosed | herein or otherwise known in the art. | Natural killer (NK) cells are large | granular lymphocytes that have        | cytotoxic activity but do bind    | antigen. NK cells show antibody- |
|                                      |                                      |                                    |                                     |                                     |                                       |                                   |                                        |                                      |                                    |                                       |                                    |                                     |                                       |                                   |                                 |                                       |                                       |                                     |                                      |                                      |                                     |                                     |                                    |                                   |                                        |                                         |                                     |                                      |                                   |                                     |                                       |                                     |                                       |                                   |                                  |
|                                      |                                      |                                    |                                     |                                     |                                       |                                   |                                        |                                      |                                    |                                       |                                    |                                     |                                       |                                   |                                 |                                       |                                       |                                     |                                      |                                      |                                     |                                     |                                    |                                   |                                        |                                         |                                     |                                      |                                   |                                     |                                       |                                     |                                       |                                   |                                  |
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| Petered indications include boosing a Teel-needing immune propones, and alternatively, assponse, and alternatively, assponses, and alternatively, assponses, and attentively, assponses in the annual, annual responses. Preferred indications include amentia, practications include amentia, acute (pumplosoyie amentia (ALL), plantanogomas, articults, ALDS, plantanogomas, articults, ALDS, plantanogomas, articults, ALDS, prophoma, articults, ALDS, prophoma, articults, ALDS, prophoma, articults, ALDS, prophomas, articults, ALDS, prophomas, articults, ALDS, prophomas, articults, ALDS, and an articultural and an articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articultural articul | A highly prefixed embelment<br>of the invention includes a method<br>for stimulating the production of<br>for stimulating the production of<br>the production of the invention<br>embelment of the invention<br>includes a method for inhibiting the<br>production of IPNg. It is the production of IPNg<br>includes a method for inhibiting the<br>production of IPNg. It is the production of IPNg<br>disorders (e.g., se described blood<br>disorders (e.g., se described blood<br>disorders (e.g., se described blood<br>disorders (e.g., se described blood<br>medical productions included blood<br>disorders (e.g., se described blood<br>disorders). The production is the<br>cancer than of the production of<br>medical productions and the<br>infection (e.g., viral infections,<br>the broning grant of the production<br>and malignant ostoporous, and or as<br>and malignant ostoporous, and or as<br>described blood under "Infectious<br>Searched bloom under "Infectious<br>Searched bloom under "Infectious<br>Brasses"). Highly preferred |
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| and sha recognize anthody bound<br>on argae cells, via NK Fe receptors,<br>leading to cell-mediated cytotoxicity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | emeral role in the immune system or emeral role in the immune system proinflanced to be a system or and isomsteed to be a system or and isomsteed to be a system or and isomstee in the interest of the convects [472] and intability [412], induces managing activation; and introverse MIC expression. Assays for immunomodulatory proteins for immunomodulatory the safe of the immunomodulation assays the short of the contraction (including antipodies and agonists or antagoniss of the immunomodulation, regulate immunomodulation, regulate                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Moducion of Production of Programma using Natural Killer cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | §9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HAGAIBS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 249                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

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| indications include autoimmune disease (e.g., rheumatoid arthritis. | systemic lupus erythematosis,    | multiple sclerosis and/or as described | below), immunodeficiency (e.g., as | described below), boosting a T cell-  | mediated immune response, and    | suppressing a T cell-mediated       | immune response, boosting antibody-  | dependent immune responses,       | suppressing antibody-dependent  | immune responses, boosting innate   | immunity and immune responses, | and suppressing innate immunity and | immune responses. Additional    | highly preferred indications include | inflammation and inflammatory | disorders. Additional preferred     | indications include idiopathic     | pulmonary fibrosis. Highly           | preferred indications include       | neoplastic diseases (e.g., leukemia, | lymphoma, melanoma, and/or as | described below under             | "Hyperproliferative Disorders").     | Highly preferred indications include | neoplasms and cancers, such as, for | example, leukemia, lymphoma,        | melanoma, and prostate, breast, lung, | colon, pancreatic, esophageal,       | stomach, brain, liver and urinary | cancer. Other preferred indications | include benign dysproliferative       | disorders and pre-neoplastic        | conditions, such as, for example, | hyperplasia, metaplasia, and/or | dysplasia. Preferred indications |
| inflammatory activities, modulate                                   | mediate humoral or cell-mediated | immunity. Exemplary assays that        | test for immunomodulatory proteins | evaluate the production of cytokines, | such as Interferon gamma (IFNg), | and the activation of T cells. Such | assays that may be used or routinely | modified to test immunomodulatory | activity of polypeptides of the | invention (including antibodies and | agonists or antagonists of the | invention) include the assays       | disclosed in Miraglia et al., J | Biomolecular Screening 4:193-204     | (1999); Rowland et al.,       | "Lymphocytes: a practical approach" | Chapter 6:138-160 (2000); Gonzalez | et al., J Clin Lab Anal 8(5):225-233 | (1995); Billiau et al., Ann NY Acad | Sci 856:22-32 (1998); Boehm et al.,  | Annu Rev Immunol 15:749-795   | (1997), and Rheumatology (Oxford) | 38(3):214-20 (1999), the contents of | each of which are herein             | incorporated by reference in its    | entirety. Natural Killer (NK) cells | that may be used according to these   | assays are publicly available (e.g., | through the ATCCTM) or may be     | isolated using techniques disclosed | herein or otherwise known in the art. | Natural killer (NK) cells are large | granular lymphocytes that have    | cytotoxic activity but do bind  | antigen. NK cells show antibody- |
|                                                                     |                                  |                                        |                                    |                                       |                                  |                                     |                                      |                                   |                                 |                                     |                                |                                     |                                 |                                      |                               |                                     |                                    |                                      |                                     |                                      |                               |                                   |                                      |                                      |                                     |                                     |                                       |                                      |                                   |                                     |                                       |                                     |                                   |                                 |                                  |
|                                                                     |                                  |                                        |                                    |                                       |                                  |                                     |                                      |                                   |                                 |                                     |                                |                                     |                                 |                                      |                               |                                     |                                    |                                      |                                     |                                      |                               |                                   |                                      |                                      |                                     |                                     |                                       |                                      |                                   |                                     |                                       |                                     |                                   |                                 |                                  |
|                                                                     |                                  |                                        |                                    |                                       |                                  |                                     |                                      |                                   |                                 |                                     |                                |                                     |                                 |                                      |                               |                                     |                                    |                                      |                                     |                                      |                               |                                   |                                      |                                      |                                     |                                     |                                       |                                      |                                   |                                     |                                       |                                     |                                   |                                 |                                  |

| include anemia, puncytopenia, theoperia, incheperia, i |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| independent falling of tumor cells and also recognize annoby bound on target cells, via NK Fe receptors, leading to cell-mediated cyntoxicity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | wassy for the regulation (i.e., and says) for the regulation (i.e., increases or decreases) of viability or and proliferation of cells in vitro new well-known in the art and may be used a rountinely modified to assess the shilisy of polyperpidises of the invertion of prolifering anthodies and agonise or antiquines of the properties of the invertion of regulates viability and profilerated of the callines of the cample, the cample of the formation of the following and the cell intensity of the antipolation of the following of the present which signals the measure the number of viable cells in measure the number of viable cells in measure the number of viable cells in the present which signals the cells. The present which signals the cells. The state of the properties of the cells. |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | F59                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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|                                                                                                    | Highly preferred indications include inflammation and Highly preferred indications include inflammation and Highly discreted indications include blood disorders (e.g., as described below disorders (e.g., as described below disorders). Highly preferred indications include Disorders', Highly preferred indications include cyrlemanois, multiple sciencis ecyclemanois, multiple sciencis and/or as described below). An additional highly preferred indication is include experimentally and immunodificiencies (e.g., as a forestribed below). An additional highly preferred indications include more experimental and an infections disease as described below in infections disease as described below possible disease (e.g. melanoma, leuternia, lymphoma, and or as described below possibles disease (e.g. melanoma, leuternia, lymphoma, and consistent described speciment indications include prosistent described indications include prosistent described speciment, lymphoma, and prosistent, breast, lung, colon.  Fighly preferred indications include prosistent described speciment, lymphoma, and prosistent, breast, lung, colon.  Fighly preferred indications include benigm of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the pro | neoplastic conditions, such as, for |
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| H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety. | Assays for the activation of removarion from the management of the activation of response clement are well-known in more ripton though the DFKB response clement are well-known in modified to success the ability of Dougherholes of the invention of including anthodies and agonisis or remained near the invention of the invention of regulate VIKB transcription factors and modulate expression of immanomondalinoty genes. Exemplary assays for transcription flowing the WERB response clement in may be used or rountinely entirely applied to the form of the properties of the mode, the west of rountinely element activity of polyperpides of the invention of including authodies and agonists or antagonists of the floral and flatin. Methods in Berger et al., Gene 66:110 (1998); merriton) include assay disclosed in Berger et al., Gene 66:110 (1998); merriton in clean of all, the or well all mannology active the contents of each of within all frager et al., 249,1884-8444 (1999), the contents of each of within the therein inconted by reference in its entirety. NK cells that may be a breist incoprotated by reference publicly wailable (e.g., though the contents to the contents of the contents of the contents of the case and the case of the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the case and the ca | ATCCTM). Exemplary human NK         |
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| example, hyperplasia, metaplasia, and ord cispalsia. Preferred indications also include arenti, programalisa also include arenti, programalisa also include arenti, thrombocytopenia, Hodgelin's factors, thrombocytopenia, Hodgelin's factors, thrombocytopenia, Hodgelin's factors, thrombocytopenia, Hodgelin's factors, the planch of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the programment of the pr |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| cells that may be used according to line, which is a human natural killer line, which is a human natural killer line established from the peripheral blood of a patient with large granular lymphocytic leukemia. This L.2 dependent as appension relative cell inc has a morphology resembling that of activated NK cells.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | phosphorylation of File.1 and the control of phosphorylation of File.1 and decision of activation of File.1 and decision of activation of carcacillate signal regulated kinase (FRK). ERK pathway regulated kinase (FRK). ERK pathway regulated kinase (FRK). ERK pathway regulated cold differentiation of Calls were pretreated differentiation. Calls were pretreated differentiation. Calls were pretreated differentiation of File.1 was assided to stimulate ERK kinase. Phosphorylation of File.1 was assided to stimulate ERK kinase. Phosphorylation of File.1 was assided to stimulate ERK kinase. Phosphorylation of Elk.1 was a more protected by the continuity be used according to these assays and AIT. It is an adherent adjusted to the second and procyte cells that may be used and procyte cells that may be used and procyte cells that may be used and additional adjusted to the continuity. |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                         | asdram, allegy, hypersensitivity asdram, allegy, hypersensitivity asdram, allegy, hypersensitivity inflammatory disorders. Additional highly preferred indications include immune and hemmoyotic disorders (e.g., as described helow under (e.g., as described helow under Related Disorders), and vilsood- Related Disorders), and vilsood- Related Disorders), and vilsood- Related Disorders), and vilsood- Related Disorders'), and vilsood- related to the control of the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed related to the control programmed  |
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| mouse preadipocyte cell line that is a continuous substant of 313 flivoblast cells developed through closul solution and undergo a preadipocyte to adipose-like conversion under appropriate differentiation conditions known in the art. (Cals were differentiated to an adipose-like sonverte differentiated to an adipose-like Sate forber being used in the screen. See Green et al., Cell 3: 12-133 (1974), the contents of volticit are entirely. | this case assay, Not kineae sasays for a finear across your kineae assay. Not kineae sasays for a search are a search as a search are a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a search as a se |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Signaling Plak<br>Signaling Pathway in<br>immune cells (such as<br>cosinophils).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| response, and suppressing an cosinophil-mediated immune response.                          |                                                                                                        |                                                                              |                                                                          |                                 |                               |                                   |                               |                                       |                                  |                                    |                                         |                              |                                      |                              |                                 |                                      |                                    |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          |                                    |
|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------|-------------------------------|-----------------------------------|-------------------------------|---------------------------------------|----------------------------------|------------------------------------|-----------------------------------------|------------------------------|--------------------------------------|------------------------------|---------------------------------|--------------------------------------|------------------------------------|-----------------------------------|-------------------------------|---------------------------------------|---------------------------------------|------------------------------------|---------------------------|------------------------------------|------------------------------------|----------------------------------------|--------------------------|------------------------------------|
| MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are berein | incorporated by reference in its entirety. Exemplary cells that may be used according to those asserts | include cosinophils. Eosinophils are important in the late stage of allergic | reactions; they are recruited to tissues<br>and mediate the inflammatory | response of late stage allergic | reaction. Moreover, exemplary | modified to assess the ability of | polypeptides of the invention | (including antibodies and agonists or | antagonists of the invention) to | modulate signal transduction, cell | proliferation, activation, or apoptosis | in cosmophils include assays | disclosed and/or cited in: Zhang JP, | et al., "Kole of caspases in | dexamethasone-induced apoptosis | and activation of c-Jun NH2-terminal | Killase and p56 illinogen-acuvated | Clin Exp Immunol; Oct;122(1):20-7 | (2000); Hebestreit H, et al., | "Disruption of fas receptor signaling | by nitric oxide in eosinophils" J Exp | Med; Feb 2;187(3):415-25 (1998); J | Allergy Clin Immunol 1999 | Sep;104(3 Pt 1):565-74; and, Sousa | AR, et al., "In vivo resistance to | corticosteroids in bronchial asthma is | associated with enhanced | phosyphorylation of JUN N-terminal |
|                                                                                            |                                                                                                        |                                                                              |                                                                          |                                 |                               |                                   |                               |                                       |                                  |                                    |                                         |                              |                                      |                              |                                 |                                      |                                    |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          |                                    |
|                                                                                            |                                                                                                        |                                                                              |                                                                          |                                 |                               |                                   |                               |                                       |                                  |                                    |                                         |                              |                                      |                              |                                 |                                      |                                    |                                   |                               |                                       |                                       |                                    |                           |                                    |                                    |                                        |                          | _                                  |

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|---------------------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------------|--------------------------------------|-------------------|
|                                       |                               |                                 |                                 |                                       |                                      |                   |
| kinase and failure of prednisolone to | inhibit JUN N-terminal kinase | phosphorylation" J Allergy Clin | Immunol; Sep;104(3 Pt 1):565-74 | (1999); the contents of each of which | are herein incorporated by reference | in its autimotive |
|                                       |                               |                                 |                                 |                                       |                                      |                   |
|                                       |                               |                                 |                                 |                                       |                                      |                   |
|                                       |                               |                                 |                                 |                                       |                                      |                   |

10095] Table IE: Polynucleotides encoding polypeptides of the present invention can be used in assays to test for one or more biological activities. One such biological activity which may be tested includes the ability of polynucleotides and polypeptides of the invention to stimulate up-regulation or down-regulation of expression of particular genes and proteins. Hence, if polynucleotides and polypeptides of the present invention exhibit activity in altering particular gene and protein expression patterns, it is likely that these polynucleotides and polypeptides of the present invention may be involved in, or capable of effecting changes in, diseases associated with the altered gene and protein expression profiles. Hence, polynucleotides, polypeptides, or antibodies of the present invention could be used to treat said associated diseases.

[1096] TAQMAN® assays may be performed to assess the ability of polynucleotides (and polypeptides they encode) to alter the expression pattern of particular "target" genes. TAQMAN® reactions are performed to evaluate the ability of a test agent to induce or repress expression of specific genes in different cell types. TAQMAN® gene expression quantification assays ("TAQMAN® assays") are well known to, and routinely performed by, those of ordinary skill in the art. TAQMAN® assays are performed in a two step reverse transcription / polymerase chain reaction (RT-PCR). In the first (RT) step, cDNA is reverse transcribed from total RNA samples using random hexamer primers. In the second (PCR) step, PCR products are synthesized from the cDNA using eene specific primers.

To quantify gene expression the TAQMAN® PCR reaction exploits the 5' nuclease activity of AMPLITAQ GOLD® DNA Polymerase to cleave a TAQMAN® probe (distinct from the primers) during PCR. The TAQMAN® probe contains a reporter dye at the 5'-end of the probe and a quencher dye at the 3' end of the probe. When the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of interest is present, the probe specifically anneals between the forward and reverse primer sites. AMPLITAQ GOLD® DNA Polymerase then cleaves the probe between the reporter and quencher when the probe hybridizes to the target, resulting in increased fluorescence of the reporter (see Figure 2). Accumulation of PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye.

[4098] After the probe fragments are displaced from the target, polymerization of the strand continues. The 3'-end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. The increase in fluorescence signal is detected only if the target sequence is complementary to the probe and is amplified during PCR. Because of these requirements, any nonspecific amplification is not detected.

[10099] For test sample preparation, vector controls or constructs containing the coding sequence for the gene of interest are transfected into cells, such as for example 293T cells, and supernatants collected after 48 hours. For cell treatment and RNA isolation, multiple primary human cells on human cell lines are used; such cells may include but are not limited to, Normal Human Dermal Fibroblasts, Aortic Smooth Muscle, Human Umbilical Vein Endothelial Cells, HepG2, Daudi, Jurkat, U937, Caco, and THP-1 cell lines. Cells are plated in growth media and growth is arrested by culturing without media change for 3 days, or by switching cells to low serum media and incubating overnight. Cells are treated for 1, 6, or 24 hours with either vector control supernatant or sample supernatant (or purified/partially purified protein preparations in buffer). Total RNA is isolated: for example, by using Trizol extraction or by using the Ambion

RNAqueous #-4PCR RNA isolation system. Expression levels of multiple genes are analyzed using TAQMAN®, and expression in the test sample is compared to control vector samples to identify genes induced or repressed. Each of the above described techniques are well known to, and routinely performed by, those of ordinary skill in the art.

[1010] Table 1E indicates particular disease classes and preferred indications for which polynucleotides, polypeptides, or antibodies of the present invention may be used in detecting, diagnosing, preventing, treating and/or ameliorating said diseases and disorders based on "target" gene expression patterns which may be up- or down-regulated by polynucleotides (and the encoded polypeptides) corresponding to each indicated eDNA Clone ID (shown in Table 1E, Column 2).

piol I Thus, in preferred embodiments, the present invention encompasses a method of detecting, diagnosing, preventing, treating, and/or ameliorating a disease or disorder listed in the "Disease Class" and/or "Preferred Indication" columns of Table IE; comprising administering to a patient in which such detection, diagnosis, prevention, or treatment is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, diagnose, prevent, treat, or ameliorate the disease or disorder. The first and second columns of Table ID show the "Gene No." and "cDNA Clone ID No.", respectively, indicating certain nucleic acids and proteins (or antibodies against the same) of the invention (including polynucleotide, polypeptide, and antibody fragments or variants thereof) that may be used in detecting, diagnosing, preventing, treating, or ameliorating the disease(s) or disorder(s) indicated in the corresponding row in the "Disease Class" or "Preferred Indication" Columns of Table IE.

[0102] In another embodiment, the present invention also encompasses methods of detecting, diagnosing, preventing, treating, or ameliorating a disease or disorder listed in the "Disease Class" or "Preferred Indication" Columns of Table IE; comprising administering to a patient combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in the "Disease Class" or "Preferred Indication" Columns of Table IE.

[1018] The "Disease Class" Column of Table 1E provides a categorized descriptive heading for diseases, disorders, and/or conditions (more fully described below) that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

The "Preferred Indication" Column of Table 1E describes diseases, disorders, and/or conditions that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

The "Cell Line" and "Exemplary Targets" Columns of Table 1E indicate particular cell lines and target genes, respectively, which may show altered gene expression patterns (i.e., up- or down-regulation of the indicated target gene) in TAQMAN® assays, performed as described above, utilizing polynucleotides of the cDNA Clone ID shown in the corresponding row. Alteration of expression patterns of the indicated "Exemplary Target" genes is correlated with a particular "Disease Class" and/or "Preferred Indication" as shown in the corresponding row under the respective column headings.

[0106] The "Exemplary Accessions" Column indicates GenBank Accessions (available online through the National Center for Biotechnology Information (NCBI) at www.ncbi.nlm.nih.gov/) which correspond to the "Exemplary Targets" shown in the adiacent row.

10107] The recitation of "Cancer" in the "Disease Class" Column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof) may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate neoplastic diseases and/or disorders (e.g., leukemias, cancers, etc., as described below under "Hyperpoliferative Disorders").

10108] The recitation of "Immune" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperpoliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity" "Cardiovascular Disorders" and/or "Blood-Related Disorders"), and infections (e.g., as described below under "Infectious Disease").

The recitation of "Angiogenesis" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant therof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), diseases and/or disorders of the cardiovascular system (e.g., as described below under "Cardiovascular Disorders"), diseases and/or disorders involving cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level"), diseases and/or disorders involving angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity"), to promote or inhibit cell or tissue regeneration (e.g., as described below under "Regeneration"), or to promote wound healing (e.g., as described below under "Wound Healing and Enithelial Cell Proliferation").

[0110] The recitation of "Diabetes" aim the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diabetes (including diabetes mellitus types I and II), as well as diseases and/or disorders associated with, or consequential to, diabetes (e.g. as described below under "Endocrine Disorders," "Renal Disorders," and "Gastrointestinal Disorders").

| Table 1E    |                  |                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                        |                      |                                                   |
|-------------|------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------------------|---------------------------------------------------|
| Gene<br>No. | cDNA<br>Clone ID | Disease<br>Class | Preferred Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Cell Line              | Exemplary<br>Targets | Exemplary<br>Accessions                           |
| 105         | HJACG02          | Diabetes         | A highly preferred indexino is dishers. Additional highly preferred indications is dishers. Additional highly preferred indications include complications associated with dishers (e.g. disherd retroporably, identic properties of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the company of the | (4D)-09/01/01          | PepCKI               | 36380<br>36380<br>gbl.05144 HUMP<br>HOCAR         |
| 105         | HJACG02          | Diabetes         | A highly preferred indication is dishers. Additional highly preferred indications is dishers. Additional highly preferred indications are always associated with dishers (e.g. dishers retrievably dishers; propropsity, felong disease, reant lailure, respiropably, dishers in the property. For earth disease, serion below), dishers nemopathy, never disease and nevre disease, smoke, importance (e.g., due to dishertic neuropathy, hood vessel blockage), serious, mental collision, dishers disease, smoke, importance (e.g., due to dishertic neuropathy, hood vessel blockage), serious, entral doilision, diswasters, production in pryerglycemic-lyperconnier promise, cultions callented and inchestion for the attention of the property and disorders as described in the "Curtionseculin.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Adipocytes-<br>3/12/01 | CAP<br>Hexokinase II | gb/AF136380/AF1<br>36380<br>gb/Z46354 HSHKE<br>X1 |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | gbix90563 HSPPA<br>RGAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | gb U91844 CFU91<br>844                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | IRSI<br>PPARG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Glucose6<br>phosphatase                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | AOSMC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Liver                                                                                                                                                                                                                                                                                                                                                                            |
| Disorder, "setion though, dy-displacing, endocrine disorders (sa described impairer, "setion below), desiplacing, endocrine disorders (set disorders, setion below), neuropathy, vision impairement (e.g., displaci retiropathy and blankerss), tuces and inspatied wound facilities, and infection (e.g., disclose instances and disorders as described in the "infections Disosaes, section below, especially of the uninty vited and shift). Highly perfected infutionis also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss, as well as complications insociated with obesity, weight gain, and weight loss, as well as complications insociated with obesity, weight gain, and weight loss, as well as complications insociated with obesity weight gain, the weight gain, and weight loss, and state of the second control of the devoc mentioned conditions, disorders, and pissuess. | A highly predicted indication is diabete. Additional highly predicted indications includes on subclications associated with diabetes (e.g., diabetic retripophy), diabetic nephropaphy, ticky diseased; diseased; diabetic retripophy diabetic repropripations, diseased; and in the "Recall Episoders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., die no diabetic neuropathy). Bood vessel blockage, heart disease, smoke, importence (e.g., due to diabetic neuropathy, nerve disease and nerve lossess, smoke, importance (e.g., due to diabetic neuropathy, nerve disease heart disease, smoke, mantal confinion, divensions, and nerve disease, smoke, importance (e.g., due to diabetic neuropathy or blood vessel blockage), seztrues, heart dioentic care, endrowascular disease; de, heart disease, adtronosteries, saction below), destriportion, and disearche (e.g. disearches assertion below), parapitudine, anderorine disease; described in the "Endocrine Disearches" sextion below), neuropathy, vision in the "Interiors Diseases' sextion below), neuropathy, vision in the "Interiors Diseases' sextion below, neuropathy, vision mantal and infection (e.g. infections diseases and disearches as described in the "Mischine Rossess" sextion below, especially of the minny visit and affection (e.g. infections diseases and disearches and visional to the survention include methods of preventing, detecting, disaposing, treating and/or aurelineaning the abover mentioned conditions, disearchs, and diseases, do diseases, AOSMC cells are human aorits smooth muscle cells). | A highly preferred indication is diabetes. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal faither, nephropathy, and/or other diseases and disorders as eleaenbed in the "Renal nephropathy and/or other diseases and disorders as eleaenbed in the "Renal |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Diabetes                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HJACG02                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 105                                                                                                                                                                                                                                                                                                                                                                              |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | gb/X06990 HSICA<br>M1<br>gb/X04403 HS26K<br>DAR<br>gb/M29474 HUMR<br>AGI                                                                                                                                                                                                                                                                                                                                                                                                                                | gelAJ300189 HSA<br>30018<br>gelX02532 HSIL1<br>BR<br>gelX12705 HSBC<br>DF1A<br>gelAJ270944 HSA<br>gelAJ270944 HSA<br>gelAJ309221A30922                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | gb M29474 HUMR<br>AG1                                                                                                                    |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ICAM<br>116<br>Rag1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | CD30<br>CD40<br>IL1B<br>IL5<br>TNF<br>VCAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Rag1                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Adipocytes-<br>3/12/01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | AOSMC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Caco-2                                                                                                                                   |
| Broaders' section to below), dishedren menyaphty, prave disease and never demage (e.g., due to directic menyaphty), blood vessel blockage, heart disease, studie, impetuenc' (e.g., due to directic menyaphty or hond vessel blockage), sections, manual diversional, divositions, annotation of hyporglycenic-lopporasonale coma, cardiovascular disease; (e.g., heart disease, alternod-learness, microvascular disease), (e.g., heart disease, alternod-learness), microvascular disease, permoderically, and control and an anticological disease, permoderically, and learness, and diseaders as described in the "Cardiovascular other Section Below), despitionalistic archordine disease; and essential in the "Hadorine Diseaders' section below), a manopality, vision in the "Hadorine Diseaders' section below), a manopality, vision may offen and breakers and diseases and diseases and diseased section learner in the "Infections Diseases", section below, especially of the witness of the disease, and weight loss, as well as complications associated with overging winds methods of preventing, detecting, diagnosing, teating mortalion middle methods of preventing, describing, and diseases. | despity perfective disclarations include immunological disorders south as described herein under the heading "Immuno, Activity" andore 'Bland-Reided Disorders' (particularly including but not limited to, immune described including adaptions, bil high protected menodiments on the invention include methods of preventing, cletcing, diagnosing, reading method or mathering adsorders of the immune system (or including) analoling, but not limited to, immune disorders involving adipocytes). | described herein under the heading "Immunological disorders such as described herein under the heading "Immuno, Activity" andor "Blood-Reided Disorders Growten der Berland in Standers system (e.g. hummune factivity" and the sufforwarders system (e.g. heart, lungs, circulatory system). Highly preferred embedienens of the moreinon include methods of preventing, electring, diagnosing, treating andor machineating disorders of the immune system (particularly including, but not limited to, immune disorders involving mused issues or flee enrichosecular system). (AOSMC cells are human notice smooth musele cells). | Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood- |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Immunc                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Immune                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HJACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HJACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HJACG02                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 105                                                                                                                                      |

| ing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | thas Daudi ICAM Regil mmc VCAM of the VCAM coding                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | h as HEK293 c-maf                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Highly preferred indications include immunological disordexe such as described between darket included in the bedding "Human Activity" andro" "Blood-described bedding "Human Activity" andro" "Blood-described including the man Activity and andro "Blood-described "Gentellarly unablanding," but not limited to, minume disorders involving endodatial cells). Highly preferred embodiments of the invention include methods of preventing, detecting, describing, describing, describing, describing, describing, describing, describing, describing, describing, describing and or anchorating disorders of the immune system (particularly methods) but not limited to, minume disorders involving endobletial cells). (HUVEC cells are human unablitials wein endobletial cells). |         |
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| Related Disorders" (particularly including, but not limited to, immulsidenches movivilian text). Highly speciered embodiving the cells for the gastoniciarisal race). Highly preferred embodiments of the invention include methods of prevent detecting, diagnosing, treating and/or ambiencating disorders of the immunes system (particularly including, but not limited to, immune disorders involving cells of the gastroninessinal tract). The Caro-Jine is a human colorectal adelencarionan cell line available through ATCCPM, as cell line number HTB-37). | Highly preferred indications include immunological disorders sus-<br>ble carried the extraction of the control of the control of the<br>Related Disorders" (pratricularly including but not limited to, im-<br>disorders involving the Pecchle). Highly operated embodiments<br>including include methods of preventing, detecting, disposing,<br>made in methods in readules of preventing, detecting, disposing,<br>including but not limited to, immune disorders involving Pecchle<br>including but not limited to, immune disorders involving Pecchle<br>Drandf cell line is a human Byrmpholist cell line available throw<br>ATCCPs as cell line number (CL23). | Highly preferred indications include immunological disordexs such<br>described hevein under the beading Furnames Activity* and/or "Bl<br>Related Disordess" (particularly including, but not limited to, inm<br>disorders involving epithical cells on the reun system). Highly pur-<br>table dispossing, treating and or machine disorders of the immune<br>oparticularly including, but not limited to, immune disorders immune<br>oparticularly including, but not limited to, immune disorders invol-<br>prited and cells or the renal system). (The 293 cell line is subman<br>embryonal kelary epithical cell line available through the ATCC<br>ed line number (281-1573). | Highly preferred indications include immunological disorders such descarcibe therein under the breading "Immune Activity" and or 'Blot descarcibe therein under the breading "Immune Activity" and or 'Blot Related Disorders' (particularly including, but not limited to, mmu beis sixeders). The control of the properties of the immune of the growth and activity and activities and or arceliorating disorders of the immune system (particularly including and or mentioning disorders of the immune system (particularly including clothers).                                                                                                                                                                                                                                     | W. 1    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Immune d                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Immune H                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Immune P                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HJACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HJACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HJACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | TIACCON |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 105     |

| gblAJ270944 HSA<br>27094                                                                                                                                                                                                                                                                                                                                                                                                                                          | gb M29474 HUMR<br>AG1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | gb X17254 HSERY<br>FI<br>gb X12705 HSBC<br>DFIA<br>gb AJ270944 HSA<br>27094                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | gb A30922 A30922                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | gb AJ300189 HSA<br>30018                                                                                                                                                                                       |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Rag 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | GATAI<br>ILS<br>TNF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | VCAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | CD40                                                                                                                                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | NHDF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | U937                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | AOSMC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Daudi                                                                                                                                                                                                          |
| Related Disorders' (retrictably including but not limited to immune disorders involving T-cells). Highly preferred embediments of the meetine include methods of preventing, detecting, diagnosting, tensing moder amedicating disorders of the immune system of particularly including, but not limited to, immune disorders involving T-cells, (The Judac cell line is a human T jumphosyte cell line available through the ATCCPA as cell line number TH-152). | Highly prefrared indications include immunological disorders such as described beein under the heading "Immuno Activity" audio" Blood-Related Disorders' (particularly including, but not limited to, immune disorders' involving the skilly. Highly including, but not limited to, immune indicates involving the skilly. Highly relevant prefrared embodiments of the invention include methods of preventing, detecting, disaposing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune desarders involving the skin). (WHIP cells are normal human dermal flivohists). | Highly preferred indections include immunological disorders such as<br>described berein under the beading "Immune Activity" and/or "Blood-<br>Related Disorders" (tensicality including but not limited to, immane<br>disorders involving monocytes). Highly preferred embodinents of the<br>invention include methods of preventing, detecting, diagnosing, reading<br>and/or ameliorating disorders of the immune system (particularly<br>including, but not limited to, immune disorders; involving monocytes).<br>(The 1993 Teell line is a human monocytes).<br>ATCCPW as cell into number (P&L.1932). | Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving mateck issues and the cardiovasatar system (e.g., beart, langs, circulatory system). Highly preferred embedients of the invention include methods of preventing, detecting, diagnosting, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving musicle issue or the cardiovascular system). (AOSMC cells are human aortic smooth musicle cells). | Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Immune                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | HIACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HACG02                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HKACD58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | HKACD58                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 105                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 110                                                                                                                                                                                                            |

|                                                                                                                                                                                                                                                                                                                                                                                                    | gb X06990 HSICA<br>M1<br>gb M29474 HUMR<br>AGI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | gb AF222342 AF2<br>22342                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | gb Z79783 HSCKR<br>L2<br>E2<br>g X17254 HSERY<br>F1<br>gb X04403 HS26K<br>DAR<br>gb A30922 A30922                                                                                                                                                                                                                                                                                                                                                                                                                                                | gb AB006967 AB0<br>06967                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|                                                                                                                                                                                                                                                                                                                                                                                                    | ICAM<br>Rag1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | CD28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | CXCR3<br>GATA1<br>116<br>VCAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | CIS3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                    | HUVEC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Liver                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | NHDF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | THPI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| disorders involving the B-cells). Highly preferred embodiments of the invention include models of preventing, detecting, diagnosting, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving B-cells). (The Dand cell line as tummen Bymphoblast cell line available through the ATCCPs as cell line number (CL-213). | Highly preferred indications include immunological disorders such as described berein mode the beading Timmune Activity and ord Bood-Related Disorders' (particularly including, but not limited to, immune disorders involving endodrial cells). Highly preferred embodimens of the investion include methods or preventing, detecting, dispossing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving endodrial and cells). (IIIVEC cells are burnan unabilisal voir endodrial cells). | Highly preferred indications include immunological disorders such as described been under the beading "Immune Activity" and/or "Blood-Related Disordes" (particularly including, but not limited to, immune disorders involving edisorders involving edisorders involving edisorders involving edisorders of the invention include ruchdods of preventing, detecting diagnosing, treating and/or ameliorating disorders of the immune system options all the properties of the immune system of particularly including, but not limited to, immune disorders involving occils of the heperic system). | Highly preferred indications include immunological disorders such as described beein under the beading "Immune Activity" and/or "Blood-Related Disordes" (particularly including, but not limited to, immune disorders involving the skin). Highly preferred embodiemens of the invention include methods of preventing, detecting, disagonsing, tenting and/or ameliorating disorders of the immune system (particularly including, but not limited of, immune disorders involving the skin). (VHIPF cells are normal human dermal fibroblass). | Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and of "Blood-Rained Disorders" (particularly richduling, but not limited to, immune disorders involving monocycle). Highly preferred endodiments of the invention include methods of preventing, detecting, diagnossing, treating and/or amendiorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocycles). |
|                                                                                                                                                                                                                                                                                                                                                                                                    | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                                                                                                                                    | HKACD58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 110 HKACD58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | НКАСD58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HKACD58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                                                                                                                                                                                                                                                                                                                                    | 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 110                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| gb Z22576 HSCD6<br>9GNA<br>gb AJ270944 HSA<br>27094                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | gb AB023887 AB0<br>23887                                                                                                                 | gb AB023888 AB0<br>23888                                                                                                                      |
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| CD69<br>TNF                                                                                                                                   | True Vo                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | GAPDII                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | CCR3                                                                                                                                     | CD30                                                                                                                                          |
| U937                                                                                                                                          | Z. P. C. P. P. C. P. P. C. P. C. P. P. P. C. P.                                                                                                                                                                                            | AUSSMC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | AOSMC                                                                                                                                    |                                                                                                                                               |
| (The THPI cell line is a human monocyte cell line available through the TACC's as cell line muther THB cell cell cell cell cell cell cell cel | when both control and the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the change of the chan | halpy peterran handanon as diabeses. Addunonia nighty pretractived indications include complications associated with diabetes (e.g., diabeter include complications associated with diabetes (e.g., diabeter inciputubly, dieder inciproputaly, dischore complications associated with diabetes (e.g., diabeter incipations) and diseases and diseases and diseases and arred diamage (e.g., due to diabetic neuropathy, blood vessel blockage, heart diseases, arther importance (e.g., due to diabetic neuropathy, blood vessel blockage, heart disease, sariose, importance, e.g., due to diabetic neuropathy or blood vessel blockage, heart disease, andres collections, indonvoirasion quovassa, and disease (e.g., fortif disease, e.g., fortif disease, due to adiabetic service (e.g., due to diabetic neuropathy and expenses), blockage, heart diseases, and disearders as described in the "Cardiovoscalia" or due to diabetic repropated, and beat disearders (e.g., indictions diseases and disearders (e.g., indictions diseases and disearders and metanol praticions). Blockages and impaired wound healing, and infection (e.g., indictions diseases and disearders as extent do release and external protections). Blockages and indiction described in the "Indictions Diseases scaled healthy in and weight from and weight loss, as well as complications associated with invention include methods or preventing, detecting, diagnosia; returning diseases, lockbaC cells are human aortic arond numeric cells. | Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood- | Related Disorders" (particularly including, but not limited to, immune disorders involving muscle tissues and the cardiovascular system (e.g. |
| Immune                                                                                                                                        | Disloctor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Diabeles                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Immune                                                                                                                                   |                                                                                                                                               |
| HKACD58                                                                                                                                       | nersenon                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HNINNSO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HSDSB09                                                                                                                                  |                                                                                                                                               |
| 110                                                                                                                                           | 502                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 707                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 202                                                                                                                                      |                                                                                                                                               |

| gelX03137 HSIL2<br>RG7<br>gelAJ300189 HSA<br>30018<br>gelAZ116875 AF3<br>16875<br>gelX12705 HSBC<br>DFIA<br>gelM29474 HUMR<br>AGI                                                                                                                                                                                                                                                  | gb AF055377 AF0<br>55377<br>55377<br>TA3<br>gb X06990 HSICA<br>M1<br>gb M29474 HUMR<br>AG1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | gblAJ270944 HSA<br>27094                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | gb AB006967 AB0<br>06967<br>gb M29474 HUMR<br>AG1                                                                                                                                                                                                                                                                                                                                                                              |
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| CD40<br>CTLA4<br>IL5<br>Ragil<br>VCAM                                                                                                                                                                                                                                                                                                                                              | c-maf<br>GATA3<br>ICAM<br>Rag1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | FNT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | CIS3<br>Rag1                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                                                                                    | Caco-2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Daudi                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 6Н                                                                                                                                                                                                                                                                                                                                                                                                                             |
| heart, lungs, circulatory system)). Highly preferred embodiments of the investion in fadde mobiles of preventing, detecting largenssing, treating and and a made a medicar medicarders of the immune system (particularly indebting, but not limited to, immune disorders involving muscle issue or the endorwascular system). (AOSMC cells are human aortic smooth muscle cells). | Highly preferred indications healthet immunological disorders such as described beein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the cells of the gentionitestimal treat). Highly preferred embodineans of the invention include methods of preventing, detecting, dispossing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the gestooine-stimal tract). (The Gao-2 cell line is a human obsorbed all advosancement and activities and the ATRCPA as cell intenument 1917). | Highly preferred indications include immunological absorbers such as<br>described been under the bending "limmune Activity" and/or "Bland-<br>Related Disorders" (particularly including, but not limited to, immune<br>disorders involving the Secials. Highly preferred tenocholimens of the<br>invention include methods of preventing, detecting, diagnossing, treating<br>and/or ameliorating disorders of the immune system (particularly<br>including, but not limited to, immune disorders involving extectle). The<br>Dand cell line is a human B tymphoblast cell line available through the<br>ATCCPA as cell line number CCL-213). | Highly preferred indications include immunological disorders such as described beein under the bealing Himmun Activity's andor "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating andors ameliocating disorders of the immune system (particularly). |
|                                                                                                                                                                                                                                                                                                                                                                                    | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Immune                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                    | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                                                                                                                                 | CCR3 CCR4 CCR4 CD30 CD30 CD40 CTLA GATA Reg1 TNF VCAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | CD40<br>ICAM<br>IL10<br>Rag1<br>Rag2<br>TNF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | CD69<br>IL5<br>Rantes<br>TNF                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                 | HFK293                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HUVBC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Jurkat                                                                                                                                                                                                                                                                           |
| including, but not limited to, immune disorders involving T-cells). (The H9 cell line is a human T lymphocyte cell line available through the ATCCT <sup>IM</sup> as cell line number HTB-176). | diship pretrear diactions include immunological disearces such as described herein under the heading, "lummune Activity" and/or "Blood-leaded by a charical bay including hu not limited to, immune disearces involving epithelia colls or the renal system). Highly preferred elsorders involving epithelia colls or the renal system). Highly preferred impossing traction and/or melanting glasteries of the immune system (particularly including, but not limited to, immune disearches involving embracies for ternal system). (The 293 cell line is a human embryonal kidnoy-guibellai cell line available through the ATCCPW as cell line number CRL-1573).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Highly preferred indications include immunological disorders such as experited herein under the bending "Immune Activity" and/or "Blood-Related Disorders' (particularly including that not limited to, immune desirests moving endochalited 18; Highly preferred enhodiments of the invention include methods of preventing detecting diagnosing, the method of provening detecting diagnosing, including but not limited to, immune disorders involving enhodicial cells). (HUVEC cells are human umbitical vein endochelial cells). | Highly preferred indications include immunological disorders such as described berein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the |
|                                                                                                                                                                                                 | Іттинс                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Immune                                                                                                                                                                                                                                                                           |
|                                                                                                                                                                                                 | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HSDSI309                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | HSDSB09                                                                                                                                                                                                                                                                          |
|                                                                                                                                                                                                 | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 202                                                                                                                                                                                                                                                                              |

| gb AF043341 AF0<br>43341<br>gb AJ270944 HSA<br>27094                                                                                                                                                                                                                                                                      | gb X03137 HSIL2<br>RG7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | gblAF222342 AF2<br>22342                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | gb AF222342 AF2<br>22342<br>gb A3300189 HSA<br>30018<br>gb X04403 HS26K<br>DAR                                                                                                                                                                                                                                                                                                                                                                                                                                                               | gblAF055377/AF0<br>55377<br>gblAB006967/AB0<br>06967<br>gblAJ270944 HSA<br>27094                                                                                                                                                                                                                                                                                                                                                                                                                          |
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|                                                                                                                                                                                                                                                                                                                           | CD25                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | CD28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | CD28<br>CD40<br>II6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | c-maf<br>CIS3<br>TINF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                                                                                                                                                                                                                                                           | Liver                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Molt4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | NHDF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | SK-N-MC<br>neuroblastoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| invention include methods of preventing, detecting, diagnosing, treating and/or americating instoluces of the immune system (particularly including, but not limited to, immune disorders involving T-cells, (The Jurka cell line as human Tymphocyte cell line available through the ATCCPa as cell line number TH-152). | Highly preferred indications include immunological disorders such as described been under the brading "immune Activity" andior "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving cells of the hepsite system). Highly preferred embediments of the invention include mother not preventing decicing diagnosing, treating and/or amotion enclodes of preventing decicing diagnosing, treating and/or amotion encloses of the immune system (particularly including the true full minted to, immune disorders involving cells of the beyonic system). | Highly performed indexions tumble mammological disorders such as<br>described been under the bending "Immuno logical disorders such as<br>fleated been under the bending and undirection, immune<br>disorders involving "Leady, Highly between chaotiering, disposing, immune such on the method of preventing, disecuting, disposing, treating<br>and/or amelicating, describing, disecuting, disposing, treating<br>modern amelicating, describers, the manner system particularity<br>nochabite, but not limited to, immune disorders involving "Leelis, (The<br>Model-ed elli her is human Teell line available through the ATCC" as | Highly preferred indications include immunological disorders such as described been under the heading "Immune Activity" andor "Blood-Related Disordes" (particularly including, but not limited to, immune disorders involving the skin). Highly preferred embodiments of the invention include methods of preventing, detecting, disapposing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited, in mune disorders involving the skin). (MHDF cells are normal human dermal fitholbass). | Highly per ferred indications include immunological disorders such as described herein under the heading "Immuno Activity" and/or "Blood-Related Disorders" (particularly including but not limited to, immune disorders involving the carnal nervous yeasten). Highly perfected methodinenses of the invention include methods to preventing, detecting diagnossing tenting and end another methods to preventing, detecting (particularly including, but not limited to, immune disorders intolving the |
|                                                                                                                                                                                                                                                                                                                           | Immunc                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                           | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HSDSI309                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HSDSI309                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | HSDSB09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                                                                                                                                                                                                                                                                           | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 202                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| CONTRACTOR | ,        | central nervous sytem) (The SK-N-MC neuroblastoma cell line is a cell line derived from human brain tissue and is available through the ATCCTM as cell line number HTB-10).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | i i   | ii                                                   | A DESIGNATION OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF THE PARTY OF T |
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|            | Immune   | Highly performed indections inched, mammon-logical disorders search as<br>described herein under the heading "Immune Activity" and/or "Blood-<br>Related Disorders" (practicalisty inchinging, but not limited to, immune<br>absorders involving T-cells). Highly preferred embediments of the<br>invention inchdue mobiles of preventing, detecting, diagnossing, treating<br>and/or am-disorating disorders of the immune system (particularly<br>inchinging but not limited to, immune disorders involving T-cells), (The<br>SULPT cell line; as human T-cell line).                                                                                                     | Talos | I'NF<br>VCAM                                         | gb AJ2/0944 HSA<br>27094<br>gb A30922 A30922                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HSDSB09    | Immune   | Highly prefured indications include immunological disorders such as described been under the heading "Immune Activity" and/or "Blood-Related Disorders" (rencircularly including hat not infinited to immune disorders involving monocytes). Highly preferred embediences for the invention include methods of preventing, detecting, dispossing, treating and/or markinearing detection. Highly preferred embediences to fine involution, but not limited to, immune system (particularly moduling, but not limited to, immune disorders involving monocytes). (The THP cell line is a human monocyte cell line available through the ATCCPs as cell line number THE-202). | THPI  | CCR3<br>CD40<br>GATA3<br>ICAM<br>ILS<br>Bag2<br>VCAM | 23887<br>23887<br>23887<br>26AA360189JHSA<br>26AA360189JHSGA<br>26AS36037JHSGA<br>26AS36990JHSICA<br>MI<br>26AS36930JHSICA<br>MI<br>26AS369319SBC<br>26AS36911962[AY0<br>26AS369311962]<br>26AS369311962[AY0<br>26AS369311962]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| HSDSB09    | Immune   | Highly preferred infections benduct minumological disorders such as<br>described berein under the bending "Immune Artviry" and/or "Blood-<br>Related Disorders" (particularly including, but not limited to, immune<br>disorders involving monocytes). Highly preferred embodineans of the<br>mention include methods of preventing, desceing, disagnosting, reasing<br>and/or ameliorating inductors of the minume system (particularly<br>including, but not limited to, immune disorders involving monocytes).<br>(The 1993 Teel line is a human monocytee) and the properties of the<br>ATCCPA's as cell line number (P&L.1932).                                        | U937  | ILIB                                                 | gb/X02532 HSIL1<br>BR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| HWHGZ51    | Diabetes | A highly preferred indication is diabetes. Additional highly preferred indications associated with diabetes (e.g., diabetic retinoputly, diabetic rephropatly, kidney disease (e.g., renal failure, nephropatly, kidney diseases (e.g., renal failure, prephropatly, and/or other diseases, and disorders as described in the "Renal                                                                                                                                                                                                                                                                                                                                        | Liver | GAPDH                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | gb X04403 HS26K<br>DAR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | gb M29474 HUMR<br>AG1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | CD30<br>116                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Rag1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | AOSMC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Caco-2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Disorders" section below), diabetic neuropathy, nerve disease and nerve danage (e.g., due to diabetic neuropathy, blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy, blood vessel blockage), setzures, mental ootifisiou, drowsniese, nonekedoic hlopedys-stratures, mental ootifisiou, drowsniese, nonekedoic hlopedys-personaler ooma, endiowsacialer disease, e.g., heart disease, adheroseleveris, microwacialer disease, giventerism, stroke, and obre diseases and disorders and disorders as extion below), dyslipidemia, endocrite Disorders" section below), dyslipidemia, endocrite disease, stand disorders of the fartheorier Disorders' section below), heropaphy, vision impliment (e.g., diabetic retinopathy and bindiaces), ulcers and disorders wound healing, and intechnot (e.g., inficious diseases) and disorders as described in the "infections Diseases" section below, especially of the ining virtual and short lightly preferred indictions associated with obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight does Preferred embodiments of the mention include methods of preventing detecting digmosting treating and on which remained conditions, disorders, and | Highly preferred indications include immunological disouthrs such as described herein under the heading "Immune Activity" and/or "Blood-Related Disouthes" (particularly including, but not limited to, immune disouthes involving muscle tissus and the cardiovascular system) (e.g. heart, lungs, circulatory system). Highly preferred embediments of the invention include methods of preventing, detecting, disagnosing, reasing and/or amediorating isotories of statements of the invention include methods of preventing, detecting, disagnosing, reasing and/or amediorating isotories of the immune system (particularly modeling, but not limited to, immune disagnosing tracting including, but not limited to, immune disagnosing muscle tissue or the endealwastalar system). (AOSMC cells are human aortic smooth muscle cells). | Highly preferred indications trable immunological disorders such as described been in under the heading "Immune Activity" and/or "Blood-Related Disorders" (periodiarly including, but not limited to, immune disorders involving the cells of the genomicianian trab. Highly preferred embodinemis of the invention include methods of prevaning, detecting, dispossing, trading and mentioning disorders of the immune system (periodiardy including, but not limited to, immune disorders involving cells of the gestromission little (TIC Cace-2 cell little is a human ordioeral advocariatoms cell little cachingles). |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Immme                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | GZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HWHGZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HWHGZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HWH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| Γ   |         |         | ATCCTM as call line number UTD 27)                                                                                                          |        |             |                  |
|-----|---------|---------|---------------------------------------------------------------------------------------------------------------------------------------------|--------|-------------|------------------|
| 247 | HWHGZ51 | Immune  | Highly preferred indications include immunological disorders such as                                                                        | Daudi  | CIS3        | gb AB006967 AB0  |
|     |         |         | described herein under the heading "Immune Activity" and/or "Blood-<br>Related Disorders" (narticularly including but not limited to immune | _      | CXCR3       | 06967            |
|     |         |         | disorders involving the B-cells). Highly preferred embodiments of the                                                                       |        | TOTAL TOTAL | L2               |
|     |         |         | invention include methods of preventing, detecting, diagnosing, treating                                                                    |        |             | gb X06990 HSICA  |
|     |         |         | and/or ameliorating disorders of the immune system (particularly                                                                            |        |             | Mi               |
|     |         |         | including, but not limited to, immune disorders involving B-cells). (The                                                                    | -      |             |                  |
|     |         |         | Daudi cell line is a human B lymphoblast cell line available through the ATCCTM as cell line number CCL -213)                               | _      |             |                  |
| 247 | HWHG241 | Transmo | Highly preferred indications include immunological disorders each ac                                                                        | H0     | шк          | ON 12705/HSBC    |
| ì   |         |         | described herein under the heading "Immune Activity" and/or "Rlood."                                                                        | 1      | VCAM        | DETA             |
|     |         |         | Related Disorders" (particularly including, but not limited to, immune                                                                      |        | VLA4        | gb A30922 A30922 |
|     |         |         | disorders involving the T-cells). Highly preferred embodiments of the                                                                       |        |             | gb X16983 HSINT  |
|     |         |         | invention include methods of preventing, detecting, diagnosing, treating                                                                    |        |             | AL4              |
|     |         |         | and/or ameliorating disorders of the immune system (particularly                                                                            |        |             |                  |
|     |         |         | including, but not limited to, immune disorders involving T-cells). (The                                                                    |        |             |                  |
|     |         |         | H9 cell line is a human T lymphocyte cell line available through the                                                                        |        |             |                  |
|     |         |         | ATCC <sup>TM</sup> as cell line number HTB-176).                                                                                            |        |             |                  |
| 247 | HWHGZ51 | Immune  | Highly preferred indications include immunological disorders such as                                                                        | HEK293 | Rag1        | gb M29474 HUMR   |
|     |         |         | described herein under the heading "Immune Activity" and/or "Blood-                                                                         |        | TNF.        | AGI              |
|     |         |         | Related Disorders" (particularly including, but not limited to, immune                                                                      |        |             | gb AJ270944 HSA  |
|     |         |         | disorders involving epithelial cells or the renal system). Highly preferred                                                                 |        |             | 27094            |
|     |         |         | embodiments of the invention include methods of preventing, detecting,                                                                      |        |             |                  |
|     |         |         | diagnosing, treating and/or ameliorating disorders of the immune system                                                                     |        |             |                  |
|     |         |         | (particularly including, but not limited to, immune disorders involving                                                                     |        |             |                  |
|     |         |         | epithelial cells or the renal system). (The 293 cell line is a human                                                                        |        |             |                  |
|     |         |         | embryonal kidney epithelial cell line available through the ATCCTM as                                                                       |        |             |                  |
|     |         |         | cell line number CRL-1573).                                                                                                                 |        |             |                  |
| 247 | HWHGZ51 | Immune  | Highly preferred indications include immunological disorders such as                                                                        | HUVEC  | CCR7        | gb X84702 HSDN   |
|     |         |         | described herein under the heading "Immune Activity" and/or "Blood-                                                                         |        | GATA3       | ABLR2            |
|     |         |         | Related Disorders" (particularly including, but not limited to, immune                                                                      |        | TNF         | gb X55037 HSGA   |
|     |         |         | disorders involving endothelial cells). Highly preferred embodiments of                                                                     | -      |             | TA3              |
|     |         |         | the invention include methods of preventing, detecting, diagnosing,                                                                         |        |             | gb AJ270944 HSA  |
|     |         |         | treating and/or ameliorating disorders of the immune system (particularly                                                                   |        |             | 27094            |
|     |         |         | including, but not limited to, immune disorders involving endothelial                                                                       |        |             |                  |
|     |         |         | cells). (HUVEC cells are human umbilical vein endothelial cells).                                                                           |        |             |                  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| gb M29474 HUMR<br>AGI<br>gb AY011962 AY0<br>11962                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | gb X84702 HSDN<br>ABLR2<br>gb X06990 HSICA<br>M1<br>gb A1270944 HSA<br>gb A30922 A30922                                                                                                                                                                                                                                                                                                                                                                                                                                            | gb X03137 HSIL2<br>RG7<br>gb A3170944 HSA<br>27094<br>gb A30922 A30922                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | gb/X84702 HSDN<br>ABLR2<br>gb/A3300189 HSA<br>30018<br>gb/X55037 HSGA<br>TA3<br>gb/A1270944 HSA<br>27094                                                                                                                                                                                                                                                                                                                                                                                                                                                            | gb AB006967 AB0<br>06967                                                                                                                 |
| Rag1<br>Rag2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | CCR7<br>ICAM<br>TNF<br>VCAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | CD25<br>TNF<br>VCAM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | CCR7<br>CD40<br>GATA3<br>HLA-c<br>TNF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | CIS3<br>LTBR                                                                                                                             |
| Jurkat                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Liver                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Molt4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | NHDF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | SK-N-MC<br>neuroblastoma                                                                                                                 |
| Highly preferred indexions include immunological disorders such as<br>described berein under the heading "Immuno facial disorders such as<br>the properties of the | Highly preferred indications include immunological disorders such as described been indeed the heading Himmun Activity, audior "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving eds of the bepards system). Highly preferred comboliments of the invention include mothers of preventing detecting diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the heparts, system). | Highly preferred indexions madule immunological disorders such as<br>described been under the beading "Immune Activity" and/or "Bland-<br>Related posterior" (penticularly including, but not limited to, immune<br>disorders involving T-cells). Highly preferred emboliments of the<br>mention include methods of preventing, detecting, diseased, it enable<br>and/or ameliorating indexides of the immune system (particularly<br>including, but not limited to, immune disorders involving T-cells, (The<br>Molet-deed line is a human T-cell line available through the ATCC <sup>TM</sup> as<br>cell line number CRL-1882). | Highly preferred indications handle atmostogical disorders such as<br>described berein under the bending "Immune Activity" and/or "Blaod-<br>Related Disorders" (remicellarly including, but not limited to, immune<br>disorders involving the skin). Highly preferred embodiemes is of the<br>mention include methods of preventing, detecting, disagnosing, treating<br>and/or ameliorating indicates the immune system furtherlandy<br>including, but not limited to, immune disorders involving the skin).<br>(NHDF cells are normal human dermal fibroblasss). | Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood- |
| Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Immune                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Immune                                                                                                                                   |
| HWHGZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HWHGZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HWHGZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HWHGZ51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HWHGZ51                                                                                                                                  |
| 247                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | [WH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HW                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | MH .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HA                                                                                                                                       |

|     |         |         | Related Disorders" (particularly including, but not limited to, immune disorders involving the central nervous system). Highly preferred                                                                                                                                                          |      | Rag1  | gb AK027080 AK0<br>27080 |
|-----|---------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-------|--------------------------|
|     |         |         | embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or methodrating favortes of the immune system (particularly including, but not limited to, immune disorders involving the central nervous system). (The SK-N-MC neuroblastoma cell line is a cell |      |       | gb M29474 HUMR<br>AGI    |
|     |         |         | line derived from human brain tissue and is available through the ATCCTM as cell line number HTB-10).                                                                                                                                                                                             |      |       |                          |
| 247 | HWHGZ51 | Immunc  | Highly preferred indications include immunological disorders such as                                                                                                                                                                                                                              | SUPT | CCR4  | gb AB023888 AB0          |
|     |         |         | described herein under the heading "Immune Activity" and/or "Blood-<br>Related Disorders" (narticularly including but not limited to immune                                                                                                                                                       |      | Kag1  | 23888<br>ahlM70474HTTMR  |
|     |         |         | disorders involving T-cells). Highly preferred embodiments of the                                                                                                                                                                                                                                 |      |       | AGI                      |
|     |         |         | invention include methods of preventing, detecting, diagnosing, treating                                                                                                                                                                                                                          |      |       | gb AJ270944 HSA          |
|     |         |         | and/or ameliorating disorders of the immune system (particularly                                                                                                                                                                                                                                  |      |       | 27094                    |
|     |         |         | including, but not limited to, immune disorders involving T-cells). (The                                                                                                                                                                                                                          |      |       |                          |
| 247 | HWHG251 | Immonia | SOLI COLINICIS a numan 1-CCI IIIC).  Highly wedered indications include immunological disorders each as                                                                                                                                                                                           | тны  | -maf  | 051 A ED 553771 A ED     |
| ì   |         |         | described herein under the heading "Immune Activity" and/or "Blood-                                                                                                                                                                                                                               |      | CCR7  | 55377                    |
|     |         |         | Related Disorders," (narticularly including but not limited to immune                                                                                                                                                                                                                             |      | CXCR3 | WCINE SHINE              |
|     |         |         | disorders involving monocytes). Highly preferred embodiments of the                                                                                                                                                                                                                               |      | IL5   | ABLR2                    |
|     |         |         | invention include methods of preventing, detecting, diagnosing, treating                                                                                                                                                                                                                          |      |       | gb Z79783 HSCKR          |
|     |         |         | and/or ameliorating disorders of the immune system (particularly                                                                                                                                                                                                                                  |      |       | 175                      |
|     |         |         | including, but not limited to, immune disorders involving monocytes).                                                                                                                                                                                                                             |      |       | gb[X12705]HSBC           |
|     |         |         | (The THP1 cell line is a human monocyte cell line available through the ATCCTM as cell line number TIB-202).                                                                                                                                                                                      |      |       | DFIA                     |
| 247 | HWHGZ51 | Immune  | Highly preferred indications include immunological disorders such as                                                                                                                                                                                                                              | U937 | 69CD  | gb Z22576 HSCD6          |
|     |         |         | described herein under the heading "Immune Activity" and/or "Blood-                                                                                                                                                                                                                               |      | ICAM  | 9GNA                     |
|     |         |         | Related Disorders" (particularly including, but not limited to, immune                                                                                                                                                                                                                            |      | TNF   | gb X06990 HSICA          |
|     |         |         | disorders involving monocytes). Highly preferred embodiments of the                                                                                                                                                                                                                               |      |       | Mi                       |
|     |         |         | invention include methods of preventing, detecting, diagnosing, treating                                                                                                                                                                                                                          |      |       | gb AJ270944 HSA          |
|     |         |         | and/or ameliorating disorders of the immune system (particularly                                                                                                                                                                                                                                  |      |       | 27094                    |
|     |         |         | including, but not limited to, immune disorders involving monocytes).                                                                                                                                                                                                                             |      |       |                          |
|     |         |         | (The U937 cell line is a human monocyte cell line available through the                                                                                                                                                                                                                           |      |       |                          |
|     |         |         | ATCC <sup>TM</sup> as cell line number CRL-1593.2).                                                                                                                                                                                                                                               |      |       |                          |

results of comparisons to protein and protein family databases. The first column provides a unique clone identifier, "Clone ID NO.", corresponding to a cDNA clone disclosed in Table IA and/or Table IB. The second column provides the unique contig identifier, "Contig ID:" which allows correlation with the information in Table IB. The third column provides the sequence identifier, "SEQ ID NO.", for the contig polynucleotide sequences. The fourth column provides the snayisis method by which the omology/identity disclosed in the Table was determined. The fifth column provides a description of the PFAM/NR hit identified by each analysis. Column six provides the accession number of the PFAM/NR hit disclosed in the lifth column. Column seven, score/percent identity, provides a quality score or the percent identity, of the hit disclosed in column five. Comparisons were made between polypeptides encoded by polynucleotides of the invention and a non-redundant protein database (herein referred to as "NR"), or a database of protein families fherein referred to as "PFAM/N, as described below.

The NR database, which comprises the NBRF PIR database, the NCBI GenPept database, and [0112] the SIB SwissProt and TrEMBL databases, was made non-redundant using the computer program nrdb2 (Warren Gish, Washington University in Saint Louis), Each of the polynucleotides shown in Table 1B. column 3 (e.g., SEO ID NO:X or the 'Ouery' sequence) was used to search against the NR database. The computer program BLASTX was used to compare a 6-frame translation of the Ouery sequence to the NR database (for information about the BLASTX algorithm please see Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish and States, Nat. Genet. 3:266-272 (1993). A description of the sequence that is most similar to the Query sequence (the highest scoring 'Subject') is shown in column five of Table 2 and the database accession number for that sequence is provided in column six. The highest scoring 'Subject' is reported in Table 2 if (a) the estimated probability that the match occurred by chance alone is less than 1.0e-07, and (b) the match was not to a known repetitive element. BLASTX returns alignments of short polypeptide segments of the Query and Subject sequences which share a high degree of similarity; these segments are known as High-Scoring Segment Pairs or HSPs. Table 2 reports the degree of similarity between the Query and the Subject for each HSP as a percent identity in Column 7. The percent identity is determined by dividing the number of exact matches between the two aligned sequences in the HSP, dividing by the number of Query amino acids in the HSP and multiplying by 100. The polynucleotides of SEQ ID NO:X which encode the polypeptide sequence that generates an HSP are delineated by columns 8 and 9 of Table 2.

1913] The PFAM database, PFAM version 2.1, (Sonnhammer, Nucl. Acids Res., 26:320-322, 1998))consists of a series of multiple sequence alignments; one alignment for each protein family. Each multiple sequence alignment is converted into a probability model called a Hidden Markov Model, or HMM, that represents the position-specific variation among the sequences that make up the multiple sequence alignment (see, e.g., Durbin, et al., Biological sequence analysis: probabilistic models of proteins and nucleic acids, Cambridge University Press, 1998 for the theory of HMMs). The program HMMER version 1.8 (Sean Eddy, Washington University in Saint Louis) was used to compare the predicted protein sequence for each Query sequence (SEQ ID NO:Y in Table 1B) to each of the HMMs derived from PFAM

version 2.1. A IMM derived from PFAM version 2.1 was said to be a significant match to a polypeptide of the invention if the score returned by HMMER 1.8 was greater than 0.8 times the HMMER 1.8 score obtained with the most distantly related known member of that protein family. The description of the PFAM family which shares a significant match with a polypeptide of the invention is listed in column 5 of Table 2, and the database accession number of the PFAM hit is provided in column 6. Column 7 provides the score returned by HMMER version 1.8 for the alignment. Columns 8 and 9 delineate the polynucleotides of SEQ ID NO.X which encode the polypeptide sequence which show a significant match to a PFAM protein family.

[0114] As mentioned, columns 8 and 9 in Table 2, "NT From" and "NT To", delineate the polynucleotides of "SEQ ID NO:X" that encode a polyneptide having a significant match to the PFAM/NR database as disclosed in the fifth column. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polyneptide encoded by the polynucleotides of SEQ ID NO:X delineated in columns 8 and 9 of Table 2. Also provided are polynucleotides encoding such proteins, and the complementary strand thereto.

initis] The nucleotide sequence SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, the nucleotide sequences of SEQ ID NO:X are useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in ATCC<sup>TM</sup> Deposit No:Z. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to these polypeptides, or fragments thereof, and/or to the polypeptides encoded by the cDNA clones identified in, for example, Table IA and/or 1B.

[0116] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

10117] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and a predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing cDNA ATCC<sup>PM</sup> Peposit No:Z(e,g., as set forth in columns 2 and 3 oTTable 1A and/or as set forth, for example, in Table 1B, 6, and 7). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the

protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human eDNA, collecting the protein, and determining its sequence.

|                               | 777                                         | 204<br>297                                  | 68                                                                      | 1003                                     | 1114                                                  | 329                                      | 329                        | 565                     | 8 %  | 98  | 619  | 1001                                         | 522<br>634                                 | 1465                                | 76                                                                   |
|-------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------------|------------------------------------------|----------------------------|-------------------------|------|-----|------|----------------------------------------------|--------------------------------------------|-------------------------------------|----------------------------------------------------------------------|
| NT To                         | 7                                           | F & 4                                       | 13.3                                                                    | 10                                       | Π                                                     | E.                                       | 3                          | 4                       |      | 1   | 9    | 01 4                                         | 5.9                                        | 14                                  | 1797                                                                 |
| NT From                       | 10                                          | 291<br>151<br>10                            | 1306                                                                    | 470                                      | 317                                                   | 141                                      | 24                         | 454                     | - 99 | 535 | 311  | 414                                          | 641                                        | 83                                  | 109                                                                  |
| Score/<br>Percent<br>Identity | 100%                                        | 98%<br>44%<br>100%                          | 100%<br>95%                                                             | 142.7                                    | 100%                                                  | 35.6                                     | %08                        | 27%                     | 30%  | 75% | 100% | %66<br>63%                                   | %5 <i>L</i>                                | 100%                                | 100%                                                                 |
| PFam/NR Accession<br>Number   | Q9NYD1                                      | Q9NYD1                                      | pir JE0383 JE0383                                                       | PF00822                                  | Q8WUW3                                                | PF00822                                  | QSWUW3                     |                         |      |     |      | Q9UKG4                                       | Q9GMK2                                     | Q9H173                              | ОЭНССО                                                               |
| PFam/NR Description           | (Q9NYD1) G-PROTEIN-<br>COUPLED RECEPTOR 48. | (Q9NYDI) G-PROTEIN-<br>COUPLED RECEPTOR 48. | NADH dehydrogenase<br>(ubiquinone) (EC 1.6.5.3) chain<br>NDUFB4 - human | PFAM: PMP-<br>22/EMP/MP20/Claudin family | (Q8WUW3) Hypothetical 27.7<br>kDa protein (Fragment). | PFAM: PMP-<br>22/EMP/MP20/Claudin family | (Q8WUW3) Hypothetical 27.7 | kDa protein (Fragment). |      |     |      | (Q9UKG4) NA+/SULFATE<br>COTRANSPORTER SUT-1. | (Q9GMK2) HYPOTHETICAL<br>10.0 KDA PROTEIN. | (Q9H173) SIL1 PROTEIN<br>PRECURSOR. | (Q9HCC0) NON-BIOTIN<br>CONTAINING SUBUNIT OF<br>3-METHYLCROTONYL-COA |
| Analysis<br>Method            | WUblastx.6                                  | WUblastx.6<br>4                             | WUblastx.6<br>4                                                         | HMMER<br>2.1.1                           | WUblastx.6<br>4                                       | HMMER<br>2.1.1                           | WUblastx.6                 | 4                       |      |     |      | WUblastx.6<br>4                              | WUblastx.6                                 | WUblastx.6                          | WUblastx.6                                                           |
| SEQ<br>ID<br>NO:X             | 11                                          | 262                                         | 13                                                                      | 14                                       |                                                       | 263                                      |                            |                         |      |     |      | 15                                           | 18                                         | 61                                  | 21                                                                   |
| Contig ID:                    | 884134                                      | 745366                                      | 637482                                                                  | 891114                                   |                                                       | 731877                                   |                            |                         |      |     |      | 561996                                       | 635412                                     | 422672                              | 1352364                                                              |
| cDNA Clone ID                 | H2CBU83                                     | H2CBU83                                     | HACBD91                                                                 | HACCI17                                  |                                                       | HACCI17                                  |                            |                         |      |     |      | HAGAQ26                                      | HAHDB16                                    | HAICP19                             | HAJAN23                                                              |

|                              |                 | PFAM: Carboxyl transferase<br>domain                       | PF01039   | 126.6      | 294  | 617  |
|------------------------------|-----------------|------------------------------------------------------------|-----------|------------|------|------|
| W Ublastx.b (Q9H             |                 | CONTAINING SUBUNIT OF                                      | Conce     | %96<br>%16 | 557  | 1807 |
| CARBOX                       | CARB            | S-MEIHILCROIONIL-COA<br>CARBOX                             |           |            |      |      |
| WUblastx.6 (Q9JIC<br>4 SPECI | (Q9JIC<br>SPECI | (Q9JIGS) UBIQUITIN<br>SPECIFIC PROTEASE                    | Q9JIG5    | %69        | 229  | 48   |
| T                            | (FRAC           | (FRAGMENT).                                                |           |            |      |      |
| HMMER PFAN                   | PFAN            | PFAM: Diacylglycerol kinase<br>catalytic domain (presumed) | PF00781   | 22.9       | 1807 | 1956 |
| dastx.6                      | S               | (Q9NP48) PUTATIVE LIPID                                    | Q9NP48    | %86        | 1495 | 2757 |
| KIN/<br>FIS, (               | ES.             | KINASE (CDNA FLJ10842<br>FIS, CLONE NT2RP4001343           |           |            |      |      |
| WUblastx.6 (Q9)              | 3               | (Q9NP48) PUTATIVE LIPID                                    | Q9NP48    | %86        | 1503 | 2756 |
| KIN/                         | AS, SE          | KINASE (CDNA FLJ10842<br>FIS, CLONE NT2RP4001343           |           |            |      |      |
| WUblastx.6 (AAH              | (AAH            | (AAH07438) Similar to RIKEN                                | AAH07438  | 100%       | 65   | 823  |
| WIlhlactv 6 (AAF             | (AAI            | IKEN                                                       | A AH07438 | %001       | 095  | 766  |
|                              | CDN/Q           |                                                            |           | 100%       | -    | 567  |
| WUblastx.6 (Q991             | 660)            | TO                                                         | Q99KG1    | %15        | 65   | 175  |
| HETE                         | HETE            | HETEROGENEOUS                                              |           | %58        | 293  | 929  |
| NOC                          | NO.             | NUCLEAR                                                    |           | 62%        | 643  | 777  |
| (FRA                         | FR A            | RIBONUCLEOPROTEIN R<br>FRAGME                              |           |            |      |      |
| WUblastx.6 (Q9F              |                 | (Q9BZM1) GROUP XII                                         | Q9BZM1    | %66        | 251  | 817  |
|                              |                 | PHOSPHOLIPASE A2.                                          |           |            |      |      |
| WUblastx.6 (Q9E              | (O)B            | (Q9BZM1) GROUP XII                                         | Q9BZM1    | 100%       | 251  | 451  |
| SECR                         | SECR            | SECRETED PHOSPHOLIPASE A2                                  |           | 100%       | 454  | 816  |
| WUblastx 6 (O9BI             | (O9BI           | NWON MINITERIOR                                            | O9BUM1    | %66        | 109  | 804  |
|                              | (PROT           | PROTEIN FOR                                                | ļ         |            |      |      |
| IMAG                         | FRAC            | IMAGE:3050476)<br>(FRAGMENT).                              |           |            |      |      |

| E 2 12 minute ( 2.2 |         |     |             | Change of comp to the control of   | 7 00 00 00      | 1001  | 0.00 | 200  |
|---------------------|---------|-----|-------------|------------------------------------|-----------------|-------|------|------|
| HATBR65             | 635514  | 59  | WUblastx.6  | (Q96NR6) CDNA FLJ30278             | Q96NR6          | 45%   | 750  | 908  |
|                     | _       |     | 4           | fis, clone BRACE2002755.           |                 | 64%   | 617  | 751  |
| HAUAI83             | 639009  | 30  | WUblastx.6  | (BAB27250) 13 days embryo          | BAB27250        | %88   | 160  | 399  |
|                     |         |     | 4           | liver cDNA, RIKEN full-le          |                 | %06   | 25   | 84   |
|                     |         |     |             |                                    |                 | %001  | 489  | 557  |
| HAUAI83             | 383592  | 569 | WUblastx.6  | (BAB27250) 13 days embryo          | BAB27250        | 100%  | 406  | 723  |
| HRGBA60             | 1352280 | 33  | WIThlacty 6 | OSWAWS Hymothetical 22.4           | 8/1/1/80        | 100%  | 000  | 843  |
| tangara.            | 1327763 | 70  |             | kDa protein (Fragment).            | 011100          | 0/001 | 077  | Ē    |
| HBGBA69             | 709658  | 270 | WUblastx.6  | (Q8WVV8) Hypothetical 22.4         | O8WVV8          | %82   | 158  | 226  |
|                     |         |     | 4           | kDa protein (Fragment).            |                 | 100%  | 211  | 780  |
| HBGNU56             | 1352412 | 33  | WUblastx.6  | (Q96DB9) FXYD domain-              | FXY5_HUMAN      | 100%  | 125  | 637  |
|                     |         |     | 4           | containing ion transport           |                 |       |      |      |
|                     |         |     |             | regulator 5 p                      |                 |       |      |      |
| HBGNU56             | 1094642 | 271 | HMMER       | PFAM: ATP1G1/PLM/MAT8              | PF02038         | 70.5  | 475  | 609  |
|                     |         |     | 2.1.1       | family                             |                 |       |      |      |
|                     |         |     | WUblastx.6  | (Q96DB9) FXYD domain-              | FXY5_HUMAN      | 100%  | 62   | 612  |
|                     |         |     | 4           | containing ion transport           |                 |       |      |      |
|                     |         |     |             | regulator 5 p                      |                 |       |      |      |
| HBGNU56             | 1050255 | 272 | HMMER       | PFAM: ATP1G1/PLM/MAT8              | PF02038         | 70.5  | 521  | 655  |
|                     |         |     | 2.1.1       | family                             |                 |       |      |      |
|                     |         |     | WUblastx.6  | (Q96DB9) FXYD domain-              | FXY5_HUMAN      | 100%  | 125  | 658  |
|                     |         |     | 4           | containing ion transport           |                 |       |      |      |
|                     |         |     |             | regulator 5 p                      |                 |       |      |      |
| HBIAE26             | 514418  | 34  | WUblastx.6  | (AAK55521) PRO0764.                | AAK55521        | 83%   | 1009 | 974  |
|                     |         |     | 4           |                                    |                 | %59   | 983  | 744  |
| HBINS58             | 1352386 | 35  | WUblastx.6  | (Q9D6W7) 2310047N01RIK             | 2M9G6O          | 81%   | 2.5  | 578  |
|                     |         |     | 4           | PROTEIN.                           |                 |       |      |      |
| HBINS58             | 961712  | 273 | WUblastx.6  | (Q9D6W7) 2310047N01RIK<br>PROTEIN. | 2мэ <u>п</u> 6д | %08   | 71   | 589  |
| HBINS58             | 892924  | 274 | WUblastx.6  | (Q9D6W7) 2310047N01RIK             | Q9D6W7          | %6L   | 100  | 579  |
| HBJFU48             | 460392  | 36  | WUblastx,6  | (O9P195) PRO1722.                  | 561460          | 63%   | 716  | 099  |
|                     |         |     |             |                                    | ,               | 73%   | 819  | 718  |
|                     |         |     |             |                                    |                 | 64%   | 199  | 533  |
| HCE2F54             | 634016  | 39  | HMMER       | PFAM: Histone-like                 | PF00808         | 19    | 898  | 1005 |

|         |         |     | 2,1,1           | transcription factor (CBF/NF-Y) and archaeal histone                                             |                   |      |      |            |
|---------|---------|-----|-----------------|--------------------------------------------------------------------------------------------------|-------------------|------|------|------------|
|         |         |     | WUblastx.6<br>4 | (AAH07642) Unknown<br>(protein for IMAGE:3534358)<br>(Fra                                        | AAH07642          | 82%  | 298  | 1122       |
| HCE3G69 | 728432  | 40  | WUblastx.6      | (Q9H0K7) HYPOTHETICAL<br>12.4 KDA PROTEIN<br>(UNKNOWN) (PROTEIN<br>FOR MGC:303                   | Q9H0K7            | 100% | 1294 | 1647       |
| HCE3G69 | 494346  | 275 | WUblastx.6      | (Q9H0K7) HYPOTHETICAL<br>12.4 KDA PROTEIN<br>(UNKNOWN) (PROTEIN<br>FOR MGC:303                   | Q9H0K7            | 100% | 1295 | 1648       |
| HCE5F43 | 612796  | 41  | WUblastx.6<br>4 | (Q9H8M7) CDNA FLJ13397<br>FIS, CLONE PLACE1001351.                                               | Q9H8M7            | 100% | 99   | 53<br>928  |
| HCEFB80 | 1143407 | 42  | WUblastx.6<br>4 | (Q96FR3) Unknown (protein<br>for MGC:18083).                                                     | Q96FR3            | %001 | 1785 | 1979       |
| HCEFB80 | 1046853 | 276 | WUblastx.6<br>4 | (Q96FR3) Unknown (protein<br>for MGC:18083).                                                     | Q96FR3            | 100% | 1777 | 1971       |
| HCEWE20 | 543370  | 44  | WUblastx.6<br>4 | (Q9P1J1) PRO1546.                                                                                | 111460            | %6L  | 501  | 551<br>717 |
| HCFOM18 | 553582  | 45  | WUblastx.6<br>4 | (Q9H728) CDNA: FLJ21463<br>FIS, CLONE COL04765.                                                  | О9Н728            | %09  | 621  | 490        |
| HCGMD59 | 636078  | 46  | WUblastx.6<br>4 | catalase (EC 1.11.1.6) -<br>Campylobacter jejuni                                                 | pir 140767 140767 | %16  | 296  | 186        |
| HCNDR47 | 1016919 | 47  | WUblastx.6<br>4 | (BAB84904) FLJ00149 protein<br>(Fragment).                                                       | BAB84904          | 93%  | 969  | 1154 263   |
| HCNDR47 | 863677  | 277 | WUblastx.6<br>4 | (Q24333) ELASTIN LIKE<br>PROTEIN (FRAGMENT).                                                     | Q24333            | 21%  | 42   | 197        |
| HCNDR47 | 874128  | 278 | WUblastx.6<br>4 | (BAB84904) FLJ00149 protein<br>(Fragment).                                                       | BAB84904          | %86  | 148  | 333        |
| HCWDS72 | 707833  | 52  | WUblastx.6      | conserved hypothetical protein<br>PA1527 [imported] -<br>Pseudomonas aeruginosa (strain<br>PAO1) | pir D83454 D83454 | 77%  | 318  | 4          |
| HCWKC15 | 553621  | 53  | WUblastx.6      | WUblastx.6 (Q9NX85) CDNA FLJ20378                                                                | Q9NX85            | 71%  | 538  | 419        |

|         |         |     | 4               | FIS, CLONE KAIA0536.                                              |            | %95        | 710   | 699          |
|---------|---------|-----|-----------------|-------------------------------------------------------------------|------------|------------|-------|--------------|
|         |         |     |                 |                                                                   |            | 63%        | 708   | 532          |
| HCWUM50 | 639037  | 54  | WUblastx.6      | (Q9NWD1) HYPOTHETICAL                                             | IGMN6Ò     | %66        | 2     | 175          |
|         |         |     | 4               | 61.6 KDA PROTEIN.                                                 |            | 73%        | 1103  | 1303         |
| HDABR72 | 1301517 | 55  | WUblastx.6      | (Q9BTK4) UNKNOWN<br>(PROTEIN FOR MGC:4663).                       | Q9BTK4     | 100%       | 969   | 988          |
| HDABR72 | 748225  | 280 | HMMER<br>2.1.1  | PFAM: Cytochrome P450                                             | PF00067    | 21.7       | 145   | 282          |
|         |         |     | WUblastx.6      | (Q9BTK4) UNKNOWN<br>(PROTEIN FOR MGC:4663).                       | Q9BTK4     | 100%       | 069   | 881          |
| HDPBA28 | 1062783 | 99  | WUblastx.6<br>4 | (Q9UKY2) ADIPOCYTE-<br>DERIVED LEUCINE<br>AMINOPEPTIDASE.         | Q9UKY2     | %66        | 259   | 3081         |
| HDPBA28 | 866429  | 281 | HMMER<br>2.1.1  | PFAM: Peptidase family M1                                         | PF01433    | 613.6      | 228   | 1391         |
|         |         |     | WUblastx.6<br>4 | (Q9UKY2) ADIPOCYTE-<br>DERIVED LEUCINE<br>AMINOPEPTIDASE.         | Q9UKY2     | %66        | 69    | 2891         |
| HDPBI32 | 1352360 | 22  | WUblastx.6<br>4 | (O88407) NEURAL<br>MEMBRANE PROTEIN 35.                           | 088407     | %26        | 37    | 984          |
| HDPBI32 | 862851  | 282 | WUblastx.6<br>4 | (O88407) NEURAL<br>MEMBRANE PROTEIN 35.                           | 088407     | %68<br>%56 | 599   | 1051 603     |
| HDPBI32 | 590733  | 283 | HMMER<br>2.1.1  | PFAM: Uncharacterized protein family                              | PF01027    | 126.8      | 51    | 461          |
| HDPCJ91 | 740748  | 58  | WUblastx.6<br>4 | (Q9H387) PRO2550.                                                 | Z8EH6Ò     | 23%<br>56% | 2369  | 2407<br>2676 |
| HDPCL63 | 1019008 | 65  | WUblastx.6<br>4 | (Q9Y519) HYPOTHETICAL<br>42.3 KDA PROTEIN.                        | 615X6O     | %66        | 14    | 835          |
| HDPCL63 | 847045  | 284 | WUblastx.6<br>4 | (Q9Y519) HYPOTHETICAL<br>42.3 KDA PROTEIN.                        | 615X6O     | %16        | 2     | 730          |
| HDPGT01 | 771583  | 19  | WUblastx.6<br>4 | (Q9Y2B3) LCAT-LIKE<br>PROTEIN (LLPL).                             | Q9Y2B3     | 100%       | 8 264 | 262<br>1244  |
| HDPJM30 | 879325  | 63  | WUblastx.6<br>4 | (O94759) LONG TRANSIENT<br>RECEPTOR POTENTIAL<br>CHANNEL 2 (LTRPC | TRL2_HUMAN | %66        | 17    | 1633         |
| HDPJM30 | 603517  | 286 | WUblastx.6      | (094759) LONG TRANSIENT                                           | TRL2 HUMAN | %68        | 416   | 1312         |

|         |         |            | 4               | RECEPTOR POTENTIAL                                                           |          | %96                                     | 378                                         | 530                                          |
|---------|---------|------------|-----------------|------------------------------------------------------------------------------|----------|-----------------------------------------|---------------------------------------------|----------------------------------------------|
|         |         |            |                 | CHANNEL 2 (LTRPC                                                             |          | %86                                     | -                                           | 378                                          |
| HDPND46 | 637586  | 64         | WUblastx.6<br>4 | (Q9BR26) DI257E24.3<br>(NOVEL PROTEIN)<br>(FRAGMENT).                        | Q9BR26   | %18                                     | 12                                          | 1466                                         |
| HDPOJ08 | 731863  | 9          | WUblastx.6<br>4 | (Q9H7XI) CDNA FLJ14153<br>FIS, CLONE NT2RMI000092,<br>WEARTY SIMILAR TO MITE | Q9H7X1   | 84%<br>30%<br>90%                       | 315<br>12                                   | 904<br>479<br>524                            |
| HDPPN86 | 1037893 | 99         | WUblastx.6      | (Q98VN4) HYPOTHETICAL<br>59.4 KDA PROTIEN.                                   | Q9BvN4   | 77%<br>100%<br>97%<br>42%<br>47%<br>98% | 5063<br>919<br>1942<br>4835<br>4983<br>4611 | 5194<br>1308<br>2175<br>4891<br>5045<br>4799 |
| HDPPN86 | 895711  | 287        | WUblastx.6<br>4 | (Q9BVN4) HYPOTHETICAL<br>59.4 KDA PROTEIN.                                   | Q9BVN4   | %86                                     | 606                                         | 1817                                         |
| HDPSB18 | 1043263 | <i>L</i> 9 | WUblastx.6<br>4 | (Q9NX17) CDNA FLJ20489<br>FIS, CLONE KAT08285.                               | LIXN6O   | 66%<br>46%                              | 3407                                        | 3150 2478                                    |
| HDPSB18 | 732097  | 290        | WUblastx.6      | (Q9NX17) CDNA FLJ20489<br>FIS, CLONE KAT08285.                               | O9NX17   | 41%                                     | 863                                         | 789                                          |
| HDPSH53 | 1309174 | 89         | WUblastx.6<br>4 | (Q9EPY0) CASPASE<br>RECRUITMENT DOMAIN<br>PROTISIN 9.                        | 03EPY0   | %88<br>%65                              | 262<br>1023                                 | 456<br>1184                                  |
| HDPSH53 | 1040056 | 291        | WUblastx.6      | (Q9H257) CASPASE<br>RECRUITMENT DOMAIN<br>PROTEIN 9.                         | Q9H257   | 100%<br>92%<br>25%<br>100%              | 1131<br>301<br>1518<br>1010                 | 1184<br>423<br>1610<br>1129                  |
| HDPSH53 | 882768  | 292        | WUblastx.6<br>4 | (AAH08877) Caspase<br>recruitment domain protein 9.                          | AAH08877 | %86                                     | 316                                         | 480                                          |
| HDPSP01 | 1352280 | 69         | WUblastx.6<br>4 | (Q9BR97) UNKNOWN<br>(PROTEIN FOR MGC:10763).                                 | Q9BR97   | 93% 94% 41%                             | 1671<br>184<br>2196                         | 1718<br>1674<br>2276                         |
| HDPSP01 | 689129  | 293        | WUblastx.6<br>4 | (Q9BR97) UNKNOWN<br>(PROTEIN FOR MGC:10763).                                 | Q9BR97   | %06<br>%06                              | 227<br>1078<br>1664                         | 1114<br>1668<br>1744                         |
| HDPSP54 | 744440  | 70         | WUblastx.6      | WUblastx.6 (BAB85063) CDNA FLJ23790                                          | BAB85063 | %66                                     | 2                                           | 307                                          |

|                      | 1733                                       | 1005                           | 1440                                                                      | 857              | 1001                               | 743                                                           | 921                                                           | 1419                                | 2137                                         | 1709                                                        | 1721                                                        | 1721                                                        | 2427                                                               | 866<br>106                                                                     |
|----------------------|--------------------------------------------|--------------------------------|---------------------------------------------------------------------------|------------------|------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------|----------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                      | 261                                        | 844                            | 40                                                                        | 432              | 3                                  | e,                                                            | 10                                                            | 643                                 | 2131                                         | 1611                                                        | 1623                                                        | 1623                                                        | 808                                                                | 321                                                                            |
|                      | %69<br>%08                                 | 38.9                           | 100%                                                                      | 77.2             | 100%                               | 93%                                                           | %16                                                           | 35%                                 | %69<br>%66                                   | 100%                                                        | 100%                                                        | 100%                                                        | %66                                                                | 31%                                                                            |
|                      | Q8VHE7                                     | PF00047                        | Q9Y286                                                                    | PF00854          | Q9P2X9                             | pir T43490 T43490                                             | pir T43490 T43490                                             | 093251                              | Q9BT94                                       | pir S04970 S04970                                           | pir S04970 S04970                                           | pir S04970 S04970                                           | O9NZN8                                                             | Q9UGV6                                                                         |
| fis, clone HEP21466, | (Q8VHE7) Hypothetical 67.5<br>kDa protein. | PFAM: Immunoglobulin<br>domain | (Q9Y286) QA79 MEMBRANE Q9Y286 PROTEIN, ALLELIC VARIANT AIRM-IB PRECURSOR. | PFAM: POT family | (Q9P2X9) PEPTIDE<br>TRANSPORTER 3. | hypothetical protein<br>DKFZp434A139.1 - human<br>(fragments) | hypothetical protein<br>DKFZp434A139.1 - human<br>(fragments) | (093251) ALPHA 1 TYPE1<br>COLLAGEN. | (Q9BT94) UNKNOWN<br>(PROTEIN FOR MGC:10848). | calcium-binding protein (clone<br>pMP41) - mouse (fragment) | calcium-binding protein (clone<br>pMP41) - mouse (fragment) | calcium-binding protein (clone<br>pMP41) - mouse (fragment) | (Q9NZN8) NOT2P (CCR4-<br>NOT TRANSCRIPTION<br>COMPLEX, SUBUNIT 2), | (Q9UGV6) BK445C9.3<br>(HIGH-MOBILITY GROUP<br>(NONHISTONE<br>CHROMOSOMAL) PROT |
| 4                    | WUblastx.6<br>4                            | HMMER<br>2.1.1                 | WUblastx.6                                                                | HMMER<br>2.1.1   | WUblastx.6<br>4                    | WUblastx.6<br>4                                               | WUblastx.6<br>4                                               | WUblastx.6<br>4                     | WUblastx.6<br>4                              | WUblastx.6<br>4                                             | WUblastx.6<br>4                                             | WUblastx.6<br>4                                             | WUblastx.6<br>4                                                    | WUblastx.6                                                                     |
|                      | 71                                         | 72                             |                                                                           | 73               |                                    | 47                                                            | 296                                                           | 298                                 | 75                                           | 9/                                                          | 299                                                         | 300                                                         | 11                                                                 | 78                                                                             |
|                      | 866433                                     | 812737                         |                                                                           | 630354           |                                    | 879048                                                        | 904768                                                        | 895715                              | 785879                                       | 1306984                                                     | 879009                                                      | 751707                                                      | 619852                                                             | 740750                                                                         |
|                      | HDPUH26                                    | HDPUW68                        |                                                                           | HDPWU34          |                                    | HDPXY01                                                       | HDPXY01                                                       | HDPXY01                             | HDTBV77                                      | ното 023                                                    | ното 023                                                    | ното 023                                                    | HE2DE47                                                            | HE2NV57                                                                        |

| 1359 1285<br>1524 1492<br>1484 1353                              | 1 270<br>48 146<br>269 985                   | 25 270                                                                         | 129 1151                                   | 142 996                                    | 129 497<br>449 1051                        | 63 185                          | 114 185<br>406 780                                           | 1036 1293<br>592 639<br>635 937                        | 53 253<br>237 797 | 513 944<br>9 77                                                | 601 425                                    | 4 204                                                       | 249 410                    |
|------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|---------------------------------|--------------------------------------------------------------|--------------------------------------------------------|-------------------|----------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------|----------------------------|
| %89<br>%06<br>%89                                                | 80%<br>24%<br>87%                            | 82%                                                                            | %56                                        | %66                                        | 93%<br>6                                   | 36.2                            | 100%                                                         | 100%<br>100%<br>99%                                    | %88<br>88%        | 88%<br>95%                                                     | 47%                                        | 94%                                                         | 95%                        |
| AAH07609                                                         | Q9WVT0                                       | 095772                                                                         | CAC41349                                   | CAC41349                                   | CAC41349                                   | PF01105                         | AAH23041                                                     | ОЭВОМЗ                                                 | 69ZD6O            | Q9QZH5                                                         | Q9HBN2                                     | Q9NYC6                                                      | pirl78556 178556           |
| WUblastx,6 (AAH07609) Similar to 4 hypothetical protein PRO1722. | (Q9WVT0) SEVEN<br>TRANSMEMBRANE<br>RECEPTOR. | (095772) H_NH1021A08.1<br>PROTEIN (UNKNOWN)<br>(PROTEIN FOR MGC:14607)<br>(SIM | (CAC41349) Alpha2-<br>glucosyltransferase. | (CAC41349) Alpha2-<br>glucosyltransferase. | (CAC41349) Alpha2-<br>glucosyltransferase. | PFAM: emp24/gp25L/p24<br>family | (AAH23041) Similar to RIKEN   AAH23041 cDNA 2400003B06 gene. | (Q9BQM3) DJ842G6.1.1<br>(NOVEL PROTEIN)<br>(FRAGMENT). | (Q9QZE9) ТМ6Р1.   | (Q9QZHS) PUTATIVE PHOSPHATE/PHOSPHOENO LPYRUVATE TRANSLOCATOR. | (Q9HBN2) HYPOTHETICAL<br>15.8 KDA PROTEIN. | (Q9NYC6) NEURONAL<br>SPECIFIC TRANSCRIPTION<br>FACTOR DAT1. | membrane glycoprotein M6 - |
| WUblastx.6                                                       | WUblastx.6                                   | WUblastx.6                                                                     | WUblastx.6                                 | WUblastx.6                                 | WUblastx.6                                 | HMMER<br>2.1.1                  | WUblastx.6                                                   | WUblastx.6                                             | WUblastx.6        | WUblastx.6                                                     | WUblastx.6                                 | WUblastx.6                                                  | WUblastx.6                 |
| 79                                                               | 08                                           | 81                                                                             | 83                                         | 302                                        | 303                                        | 84                              |                                                              | 85                                                     | 87                | 88                                                             | 68                                         | 06                                                          | 92                         |
| 570903                                                           | 847060                                       | 596829                                                                         | 1352337                                    | 838598                                     | 834400                                     | 684254                          |                                                              | 603533                                                 | 847073            | 566712                                                         | 534142                                     | 411345                                                      | 513669                     |
| не2Рн36                                                          | HE8DS15                                      | 690Э6ЭН                                                                        | HE90W20                                    | HE90W20                                    | HE90W20                                    | HEEAG23                         |                                                              | неомоез                                                | HFABG18           | HFABH95                                                        | HFAEF57                                    | HFCEB37                                                     | HFGAD82                    |

| 1281                         | 501               | 307                 | 265                         | 229<br>524                                                                  | 1042                                               | 1082                                 | 768               | 722                                           | 962                                                  | 601                                             | 647                                             | 1870                                        | 1598                                          | 687<br>620<br>353<br>496                           | 114                                                            |
|------------------------------|-------------------|---------------------|-----------------------------|-----------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------|-----------------------------------------------|----------------------------------------------------|----------------------------------------------------------------|
| 1448                         | 671               | 369                 | 11 253                      | 23<br>198                                                                   | 1164                                               | 1378                                 | 812<br>928        | 213                                           | 225                                                  | 17                                              | 63                                              | 1923                                        | 1362                                          | 622<br>531<br>439<br>633                           | 378                                                            |
| %\$\$                        | 54%               | 47%                 | 89%<br>100%                 | 100%                                                                        | 28%<br>50%                                         | %15                                  | %98<br>%98        | 184.6                                         | %16                                                  | %86                                             | %86                                             | 61%                                         | 46%                                           | 86%<br>66%<br>46%<br>46%                           | 94%                                                            |
| 981.060                      | 981.160           | AAKSSS21            | tr_vs O95742-01 O95742      | Q9H8P0                                                                      | 096Н6О                                             | O9N083                               | Q9P147            | PF00378                                       | AAH25104                                             | О9Н763                                          | О9Н763                                          | 6dago                                       | Q9CWA7                                        | Q96NR6                                             | Q96FV2                                                         |
| WUblastx,6 (Q9UI86) PRO0113. | (Q9U186) PRO0113. | (AAK55521) PRO0764. | ISOFORM OATL 2 OF<br>095742 | (Q9H8P0) CDNA FLJ13352<br>FIS, CLONE OVARC1002165,<br>WEAKLY SIMILAR TO 3-0 | (Q9H960) CDNA FLJ12988<br>FIS, CLONE NT2RP3000080. | (Q9N083) UNNAMED<br>PORTEIN PRODUCT. | (Q9P147) PRO2822. | PFAM: Enoyl-CoA<br>hydratase/isomerase family | (AAH25104) Similar to RIKEN<br>cDNA 1300017C12 gene. | (Q9H763) CDNA; FLJ21269<br>FIS, CLONE COL01745. | (Q9H763) CDNA: FLJ21269<br>FIS, CLONE COL01745. | (Q9BVD9) UNKNOWN<br>(PROTEIN FOR MGC:5149). | (Q9CWA7) 0610010F05RIK<br>PROTEIN (FRAGMENT). | (Q96NR6) CDNA FLJ30278<br>fis, clone BRACE2002755. | (Q96FV2) Unknown (protein<br>for IMAGE:3945715)<br>(Fragment). |
| WUblastx.6                   | WUblastx.6        | WUblastx.6          | WUblastx.6<br>4             | WUblastx.6<br>4                                                             | WUblastx.6                                         | WUblastx.6<br>4                      | WUblastx.6<br>4   | HMMER<br>2.1.1                                | WUblastx.6<br>4                                      | WUblastx.6<br>4                                 | WUblastx.6<br>4                                 | WUblastx.6<br>4                             | WUblastx.6<br>4                               | WUblastx.6                                         | WUblastx.6                                                     |
| 93                           | 306               | 94                  | 56                          | 96                                                                          | 66                                                 | 100                                  | 101               | 102                                           |                                                      | 104                                             | 307                                             | 105                                         | 107                                           | 109                                                | 111                                                            |
| 1011487                      | 874248            | 532060              | 634743                      | 545012                                                                      | 609826                                             | 701988                               | 634161            | 570262                                        |                                                      | 1003028                                         | 883427                                          | 638231                                      | 634521                                        | 520198                                             | 662329                                                         |
| HFIIN69                      | HFIIN69           | HFTUR10             | HFKFG02                     | HFTBM50                                                                     | HFXHK73                                            | HFXJX44                              | HFXKY27           | HGBHI35                                       |                                                      | HHBCS39                                         | HHBCS39                                         | HHEAA08                                     | HHFFJ48                                       | HHGBO91                                            | HHGCM76                                                        |

| 114<br>536                                                     | 1535                                  | 1706                                                      | 250<br>1192<br>1523                  | 389                                                                            | 370                                                                            | 389                                                                               | 297                                | 1212                                                          | 232                                             | 802<br>541                                                          | 794 533                                                             |
|----------------------------------------------------------------|---------------------------------------|-----------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| 378                                                            | 210                                   | 183                                                       | 8<br>1127<br>1227                    | 99                                                                             | 47                                                                             | 291                                                                               | 220                                |                                                               | ∞                                               | 137                                                                 | 129                                                                 |
| 94%                                                            | 148.9                                 | %66                                                       | 100%<br>38%<br>94%                   | %00I                                                                           | 100%                                                                           | %96                                                                               | %08                                | 100%                                                          | %86                                             | 99%<br>45%                                                          | 99%                                                                 |
| Q96FV2                                                         | PF01546                               | Q96KN2                                                    | Q9BWV3                               | 68Ш6О                                                                          | (у9нD89                                                                        | Q9UM21                                                                            | Q9D399                             | pir T08758 T08758                                             | О9Н5F8                                          | Q96LB9                                                              | О96LВ9                                                              |
| (Q96FV2) Unknown (protein<br>for IMAGE:3945715)<br>(Fragment). | PFAM: Peptidase family<br>M20/M25/M40 | (Q96KN2) Glutamate<br>carboxypeptidase-like protein<br>2. | (Q9BWV3) PROTEIN<br>KINASE NYD-SP15. | (Q9HD89) CYSTEINE-RICH<br>SECRETED PROTEIN<br>(C/EBP-EPSILON<br>REGULATED MYEL | (Q9HD89) CYSTEINE-RICH<br>SECRETED PROTEIN<br>(C/EBP-EPSILON<br>REGULATED MYEL | (Q9UM21) UDP-GLCNAC:A-<br>1,3-D-MANNOSIDE B-1,4-N-<br>ACETYLGLUCOSAMINYLT<br>RANS | (Q9D399) 6330415B21RIK<br>PROTEIN. | hypothetical protein<br>DKFZp586J0619.1 - human<br>(fragment) | (Q9H5F8) CDNA: FLJ23476<br>FIS, CLONE HSI14935. | (Q96LB9) Peptidoglycan<br>recognition protein-I-alpha<br>precursor. | (Q96LB9) Peptidoglycan<br>recognition protein-I-alpha<br>precursor. |
| WUblastx.6<br>4                                                | HMMER<br>2.1.1                        | WUblastx.6<br>4                                           | WUblastx.6<br>4                      | WUblastx.6                                                                     | WUblastx.6<br>4                                                                | WUblastx.6                                                                        | WUblastx.6<br>4                    | WUblastx.6<br>4                                               | WUblastx.6<br>4                                 | WUblastx.6<br>4                                                     | WUblastx.6                                                          |
| 310                                                            | 113                                   |                                                           | 114                                  | 115                                                                            | 311                                                                            | 116                                                                               | 313                                | 117                                                           | 118                                             | 119                                                                 | 314                                                                 |
| 383547                                                         | 695134                                |                                                           | 456466                               | 1307789                                                                        | 509948                                                                         | 895505                                                                            | 774300                             | 719729                                                        | 651337                                          | 862030                                                              | 665424                                                              |
| HHGCM76                                                        | HHPEN62                               |                                                           | HJABB94                              | HJACG02                                                                        | HJACG02                                                                        | HJACG30                                                                           | HJACG30                            | HJBCY35                                                       | HJPAD75                                         | HKABZ65                                                             | HKABZ65                                                             |

| 786 1199<br>46 186<br>125 715              | 795 1208<br>43 183<br>122 724              | 501 1814                                           | 367 459<br>197 367<br>480 1541 |                                    | 29 61<br>61 231<br>274 828         | 298 555<br>12 314                  | 178 843                                                 | 1 879                                                                        | 78 167                                  | 46 1410                                                   | 132 305                                                   | 566 673<br>293 1366 |              |
|--------------------------------------------|--------------------------------------------|----------------------------------------------------|--------------------------------|------------------------------------|------------------------------------|------------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|---------------------|--------------|
| 86%<br>28%<br>100%                         | 86%<br>28%<br>88%                          | %66                                                | 96%<br>100%<br>96%             | 72%<br>64%<br>84%                  | 72%<br>64%<br>83%                  | 80%                                | 320.5                                                   | %66                                                                          | %06                                     | 39%                                                       | 45%                                                       | 37%                 |              |
| Ф96ВН2                                     | О96ВН2                                     | Q9NVA4                                             | Q9NVA4                         | Q9CPS2                             | Q9CPS2                             | Q9CPS2                             | PF00919                                                 | Q9BWZ5                                                                       | O9BVG6                                  | pir T16084 T16084                                         | pir T16084 T16084                                         |                     |              |
| (Q96BH2) Hypothetical 34,4<br>kDa protein. | (Q96BH2) Hypothetical 34.4<br>kDa protein. | (Q9NVA4) CDNA FLJ10846<br>FIS, CLONE NT2RP4001373. |                                | (Q9CPS2) 4933428103RIK<br>PROTEIN. | (Q9CPS2) 4933428103RIK<br>PROTEIN. | (Q9CPS2) 4933428103RIK<br>PROTEIN. | PFAM: Uncharacterized protein PF00919<br>family UPF0004 | (Q9BWZ5) DJ1187J4.4 (CGI-<br>05 PROTEIN (LOC51654)<br>SIMILAR TO RAT CDK5 AC | (Q9BVG6) SIMILAR TO CGI-<br>05 PROTEIN. | hypothetical protein F16H11.1 -<br>Caenorhabditis elegans | hypothetical protein F16H11.1 -<br>Caenorhabditis elegans |                     |              |
| WUblastx.6                                 | WUblastx.6<br>4                            | WUblastx.6                                         | WUblastx.6                     | WUblastx.6                         | WUblastx.6                         | WUblastx.6                         | HMMER 2.1.1                                             | WUblastx.6                                                                   | WUblastx.6                              | WUblastx.6                                                | WUblastx.6                                                |                     |              |
| 120                                        | 315                                        | 121                                                | 316                            | 122                                | 317                                | 318                                | 123                                                     |                                                                              | 319                                     | 124                                                       | 320                                                       |                     |              |
| 1352202                                    | 552465                                     | 1352263                                            | 638238                         | 946512                             | 889258                             | 904790                             | 876571                                                  |                                                                              | 654871                                  | 1352286                                                   | 701893                                                    |                     |              |
| HKACD58                                    | HKACD58                                    | HKAEV06                                            | HKAEV06                        | HKAFT66                            | HKAFT66                            | HKAFT66                            | HKB1E57                                                 |                                                                              | HKB1E57                                 | HKFBC53                                                   | HKFBC53                                                   |                     | And distance |

| 713                    | 832                                                                    | 830<br>555                                                             | 582<br>1013<br>1256<br>480<br>966<br>1052 | 1662            | 726                                                                            | 424<br>339<br>218                                                                | 382<br>1002                                        | 1142            | 636<br>616                                                                  | 406                                          |
|------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------|-----------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------|-----------------|-----------------------------------------------------------------------------|----------------------------------------------|
| 135                    | 23                                                                     | 96                                                                     | 262<br>201<br>1107<br>271<br>532<br>954   | 1784            | 238                                                                            | 326<br>217<br>45                                                                 | 41<br>376                                          | 105             | 571<br>59                                                                   | 296                                          |
| 32%                    | %66                                                                    | 82%<br>49%                                                             | 28%<br>100%<br>98%<br>27%<br>26%<br>44%   | 73%             | 100%                                                                           | 72%<br>83%<br>100%                                                               | 100%                                               | 100%            | 95%<br>93%                                                                  | 86%                                          |
|                        | Q9UHG2                                                                 | Q9UHG2                                                                 | Qswww1                                    | Q8WY51          | Q9BQB6                                                                         | <b>9</b> в0в6                                                                    | Q9NQW2                                             | 075477          | Q96N65                                                                      | Q9NQZ1                                       |
| Caenorhabditis elegans | (Q9UHG2) PROSAAS PRECURSOR (GRANIN- LIKE NEUROENDOCRINE PEPTIDE PRECUR | (Q9UHG2) PROSAAS PRECURSOR (GRANIN- LIKE NEUROENDOCRINE PIPTIDE PRECUR | (Q8WWWI) Smoothelin-B3.                   | (Q8WY51) HC6.   | (Q9BQB6) UNKNOWN<br>(PROTEIN FOR MGC:11276)<br>(PROTEIN FOR<br>IMAGE:3455200). | (Q9BQB6) UNKNOWN<br>(PROTISIN FOR MGC:11276)<br>(PROTISIN FOR<br>IMAGE:3455200). | (Q9NQW2) PROGRESSIVE<br>ANKYLOSIS-LIKE<br>PROTEIN. | (O75477) KE04P. | (Q96N65) CDNA FLJ31349<br>fis, clone MESAN2000092,<br>moderately similar to | (Q9NQZI) HEPATOCELLULAR CARCINOMA ASSOCIATED |
| 4                      | WUblastx.6                                                             | WUblastx.6                                                             | WUblastx.6                                | WUblastx.6<br>4 | WUblastx.6                                                                     | WUblastx.6                                                                       | WUblastx.6<br>4                                    | WUblastx.6<br>4 | WUblastx.6<br>4                                                             | WUblastx.6<br>4                              |
|                        | 125                                                                    | 323                                                                    | 126                                       | 127             | 128                                                                            | 324                                                                              | 130                                                | 131             | 134                                                                         | 135                                          |
|                        | 877489                                                                 | 704088                                                                 | 625956                                    | 581399          | 1352197                                                                        | 535730                                                                           | 753742                                             | 740755          | 791828                                                                      | 1307726                                      |
|                        | HKGDL36                                                                | HKGDL36                                                                | HKISB57                                   | HKMMW74         | HLDNA86                                                                        | HLDNA86                                                                          | HLDQR62                                            | HLDQU79         | нгком                                                                       | HLQDR48                                      |

|           |         |     |                 | PROTEIN TIDS6                                                       |                   |       |           |      |
|-----------|---------|-----|-----------------|---------------------------------------------------------------------|-------------------|-------|-----------|------|
| HI ODR 48 | 619979  | 325 | WI Iblastx 6    | (AAH24408) Hynothetical 20 3                                        | AAH24408          | %59   | 54        | 572  |
|           |         | i   |                 | kDa protein (Fragment)                                              |                   | 100%  | 675       | 701  |
| HLTHR66   | 699812  | 136 | HIMMER<br>2.1.1 | PFAM: PAP2 superfamily                                              | PF01569           | 22.3  | 35        | 151  |
|           |         |     | WUblastx.6<br>4 | (Q9D4F2) 4932443D16RIK<br>PROTEIN.                                  | Q9D4F2            | 63%   | 2         | 229  |
| HLTIP94   | 1087335 | 137 | WUblastx.6<br>4 | (Q96DH6) Hypothetical 35.2<br>kDa protein.                          | 9НО96О            | %08   | 625       | 740  |
| HLTIP94   | 1047690 | 327 | HMMER<br>2.1.1  | PFAM: RNA recognition motif.<br>(a.k.a. RRM, RBD, or RNP<br>domain) | PF00076           | 143.1 | 40        | -172 |
|           |         |     | WUblastx.6<br>4 | (Q96DH6) Hypothetical 35.2<br>kDa protein.                          | 9НО96О            | %66   | 123       | 176  |
| HLWAA17   | 629552  | 138 | WUblastx.6<br>4 | (Q9NY26) IRT1 PROTEIN<br>(SIMILAR TO ZINC/IRON<br>REGULATED         | Q9NY26            | 94%   | 226<br>85 | 960  |
|           |         |     |                 | TRANSPORTER-LIK                                                     |                   |       |           |      |
| HLWBK05   | 765310  | 139 | WUblastx.6<br>4 | (Q9CUS9) 4833416109RIK<br>PROTEIN (FRAGMENT).                       | 6Sn26Ò            | 84%   | 10        | 1173 |
| HLWBY76   | 609161  | 140 | WUblastx.6<br>4 | (AAH06651) Similar to<br>hypothetical protein FLJ23153              | AAH06651          | %9L   | 9         | 1127 |
| HLYAN59   | 553507  | 328 | WUblastx.6      | (AAL79706) Hypothetical 9.4                                         | AAL79706          | %58   | 624       | 719  |
|           |         |     | 4               | kDa protein.                                                        |                   | 93%   | 639       | 728  |
| HI VES38  | 638042  | 145 | WIlblastx 6     | (O95662) POT ORF VI                                                 | 092662            | 81%   | 743       | 856  |
|           |         | •   |                 | (FRAGMENT).                                                         |                   | 72%   | 281       | 313  |
|           |         |     |                 |                                                                     |                   | 72%   | 306       | 524  |
|           |         |     |                 |                                                                     |                   | 75%   | 466       | 735  |
|           |         |     |                 |                                                                     |                   | 33%   | 145       | 243  |
| HMADK33   | 561941  | 146 | WUblastx.6      | hypothetical protein                                                | pir T47139 T47139 | 82%   | 394       | 417  |
|           |         |     | 4               | DKFZp761P2414.1 - human                                             |                   | 100%  | 152       | 232  |
|           |         |     |                 |                                                                     |                   | %46   | 228       | 395  |
| HMADS41   | 596831  | 147 | WUblastx.6      | (AAH07725) Ceroid-                                                  | AAH07725          | 95%   | 186       | 449  |
|           |         |     |                 | lipofuscinosis, neuronal 8 (epile                                   |                   | 100%  | 427       | 1041 |
| HMAMI15   | 1352406 | 148 | WUblastx.6      | (AAL84703) Citrate lyase beta                                       | AAL84703          | %66   | 4         | 1023 |

|         |         |     | 4               | subunit.                                                                 |                   |            |      |             |
|---------|---------|-----|-----------------|--------------------------------------------------------------------------|-------------------|------------|------|-------------|
| HMAMI15 | 1049263 | 329 | WUblastx.6      | (AAL84703) Citrate lyase beta<br>subunit.                                | AAL84703          | 100%       | 372  | 920         |
| HMCFY13 | 635301  | 149 | WUblastx.6      | (Q8WZ81) Chromosome 17<br>open reading frame 26.                         | Q8WZ81            | %56        | 36   | 737         |
| HMEED18 | 560775  | 151 | WUblastx.6<br>4 | (Q9H651) CDNA: FLJ22604<br>FIS, CLONE HSI04630 (BBP-<br>LIKE PROTEIN 2). | Q9H651            | %66        | 34   | 969         |
| HMSDL37 | 943996  | 154 | WUblastx.6<br>4 | (Q9H743) CDNA: FLJ21394<br>FIS, CLONE COL03536.                          | О9Н743            | %99<br>%99 | 1189 | 1497        |
| HMSDL37 | 895429  | 330 | WUblastx.6<br>4 | (Q9H743) CDNA: FLJ21394<br>FIS, CLONE COL03536.                          | О9Н743            | 64%<br>56% | 1186 | 1494        |
| HMSDL37 | 904241  | 331 | WUblastx.6<br>4 | hypothetical protein 3 - human                                           | pir E41925 E41925 | 50%        | 421  | 350         |
| HMSF126 | 560229  | 155 | WUblastx.6<br>4 | (Q14713) POT. ORF V.                                                     | Q14713            | 39%        | 1075 | 1019        |
| HMTBI36 | 1301451 | 157 | WUblastx.6      | (Q9VZF8) CG1332 PROTEIN.                                                 | 09VZF8            | 26%        | 958  | 2556        |
|         |         |     | 4               |                                                                          |                   | 36%<br>40% | 376  | 3024<br>879 |
|         |         |     |                 |                                                                          |                   | 35%        | 2341 | 2550        |
|         |         |     |                 |                                                                          |                   | 27%        | 2494 | 2622        |
|         |         |     |                 |                                                                          |                   | 40%        | 717  | 834         |
| HMTBI36 | 866466  | 333 | HMMER<br>2.1.1  | PFAM: WD domain, G-beta<br>repeat                                        | PF00400           | 45.8       | 2490 | 2600        |
|         |         |     | WUblastx.6      | (Q9VZF8) CG1332 PROTEIN.                                                 | 84ZA6O            | %95        | 156  | 2555        |
|         |         |     | 4               |                                                                          |                   | 36%        | 2487 | 3023        |
|         |         |     |                 |                                                                          |                   | 40%        | 375  | 878         |
|         |         |     |                 |                                                                          |                   | 35%        | 2340 | 2549        |
|         |         |     |                 |                                                                          |                   | 27%        | 2493 | 2621        |
|         |         |     |                 |                                                                          |                   | 40%        | 711  | 833         |
| HMVBS81 | 639203  | 158 | WUblastx.6<br>4 | (O95070) 54TMP.                                                          | 095070            | 100%       | 10   | 450         |
| HMWFT65 | 562063  | 160 | WUblastx.6      | (Q96AZ2) Similar to<br>hypothetical protein FLJ21463.                    | 7ZV96Ò            | %19        | 1342 | 1205        |
| HNFFC43 | 753337  | 162 | WUblastx.6      | (Q969J4) Lipocalin-1                                                     | Q969J4            | %16        | 319  | 453         |
|         |         |     | 4               | interacting memorane receptor                                            |                   | 0%00       | 974  | 60/         |

| 839                | 1030              | 457                                        | 861                            | 716  | 715 | 610              | 725              | 261 | 945                   | 734               | 2092                                               | 418               | 122                     | 223                      | 124             | 110   | 122 | 1674              | 1553 | 552               | 921                  | 713  | 894 | 498 | 625 | 917 | 792 | 915 | 16/ | 595 |
|--------------------|-------------------|--------------------------------------------|--------------------------------|------|-----|------------------|------------------|-----|-----------------------|-------------------|----------------------------------------------------|-------------------|-------------------------|--------------------------|-----------------|-------|-----|-------------------|------|-------------------|----------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|
| 651<br>903         | 998               | 585                                        | 596                            | 1021 | 867 | 999              | 615              | 454 | 1028                  | 616               | 1067                                               | 741               | 9                       | 17                       | 11              | 6     | 6   | 1543              | 1398 | 334               | 949                  | 645  | 844 | 331 | 353 | 828 | 721 | 781 | 258 | 401 |
| %48<br>%66         | %66<br>%96        | %59                                        | 21%                            | 23%  | 20% | 73%              | 24%              | %99 | 64%                   | 62%               | 31%                                                | %19               | 74%                     | 45%                      | 63%             | 26%   | 24% | %62               | 75%  | %92               | %95                  | %95  | 52% | 73% | %65 | 20% | %02 | 48% | %05 | 35% |
|                    | 98WXE6            | Q8WYX2                                     | AAK55521                       |      |     | O9N083           |                  |     | O9HBS7                |                   | pir A34246 A34246                                  | О9Н387            | 6S8N6O                  | ,                        |                 |       |     | O9P195            | ,    | 060448            |                      |      |     |     |     |     |     |     |     |     |
| (Lipocalin-interac | (Q8WXE6) KCCR13L. | (Q8WYX2) Hypothetical 14.1<br>kDa protein. | WUblastx.6 (AAK55521) PRO0764. |      |     | (Q9N083) UNNAMED | PORTEIN PRODUCT. |     | (O9HBS7) HYPOTHETICAL | 14.2 KDA PROTEIN. | collagen alpha 1(VIII) chain<br>precursor - rabbit | (Q9H387) PRO2550. | (O9N8S9) POSSIBLE (HHV- | 6) U1102, VARIANT A DNA, | COMPLETE VIRION | GENOM |     | (O9P195) PRO1722. |      | (O60448) NEURONAL | THREAD PROTEIN AD7C- | NTP. |     |     |     |     |     |     |     |     |
|                    | WUblastx.6        | WUblastx.6                                 | WUblastx.6                     | 4    |     | WUblastx.6       | 4                |     | WUblastx.6            | 4                 | WUblastx.6                                         | WUblastx.6        | WUblastx.6              | 4                        |                 |       |     | WUblastx.6        |      | WUblastx.6        | 4                    |      |     |     |     |     |     |     |     |     |
|                    | 164               | 165                                        | 167                            |      |     | 169              |                  |     | 170                   |                   | 172                                                | 173               | 174                     |                          |                 |       |     | 176               |      | 177               |                      |      |     |     |     |     |     |     |     |     |
|                    | 634551            | 577013                                     | 499076                         |      |     | 519120           |                  |     | 561568                |                   | 1041375                                            | 634851            | 664507                  |                          |                 |       |     | 895462            |      | 843488            |                      |      |     |     |     |     |     |     |     |     |
|                    | HNFIY77           | HNFJF07                                    | HNGEP09                        |      |     | HNGIJ31          |                  |     | HNGJE50               |                   | HNGO112                                            | HNHEU93           | HNHFM14                 |                          |                 |       |     | HNHNB29           |      | HNHOD46           |                      |      |     |     |     |     |     |     |     |     |

| 552<br>462<br>839 | 987<br>1201<br>150                                               | 992<br>544<br>1206<br>154                                        | 973<br>887<br>378<br>1187<br>138                                 | 500<br>168<br>711<br>261                                                    | 1316                                                                                                         | 218 495 377                                                                                                   | 776                                                       | 644<br>1236<br>596<br>803           |
|-------------------|------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------|
| 283<br>379<br>486 | 145<br>1091<br>7                                                 | 516<br>149<br>1096<br>11                                         | 824<br>285<br>133<br>1077                                        | 243<br>13<br>646<br>13                                                      | 282                                                                                                          | 63<br>370<br>12                                                                                               | 252                                                       | 51<br>1204<br>54<br>66              |
| 31%<br>50%<br>61% | 99%<br>29%<br>95%                                                | 94%<br>97%<br>29%<br>95%                                         | 70%<br>92%<br>84%<br>29%<br>97%                                  | 98%<br>33%<br>40%<br>96%                                                    | 137.5                                                                                                        | 23.2<br>95%<br>100%                                                                                           | 57%                                                       | 70%<br>63%<br>37%<br>31%            |
|                   | Q96F65                                                           | Q96F65                                                           | Q96F65                                                           | Q96AA3                                                                      | PF00001<br>Q9H1Y3                                                                                            | PF00001<br>Q9H1Y3                                                                                             | AAH24118                                                  | Q9XSV8                              |
|                   | (Q96F65) Similar to RIKEN<br>cDNA 0610031J06 gene<br>(Fragment). | (Q96F65) Similar to RIKEN<br>cDNA 0610031J06 gene<br>(Fragment). | (Q96F65) Similar to RIKEN<br>cDNA 0610031306 gene<br>(Fragment). | (Q96AA3) Putative<br>endoplasmic reticulum<br>multispan transmembrane prote | PFAM: 7 transmembrane<br>receptor (rhodopsin family)<br>(Q9H1V3) DJ317G22.2<br>(ENCEPHALOPSIN)<br>(PANOPSIN) | PFAM: 7 transmembrane<br>receptor (rhodopsin family)<br>(Q9H Y3) DJ3 I7G22.2<br>(ENCEPHALOPSIN)<br>(PANOPSIN) | (AAH24118) Similar to<br>Unknown (protein for<br>IMAGE:44 | (Q9XSV8) SCO-SPONDIN<br>(FRAGMENT). |
|                   | WUblastx.6<br>4                                                  | WUblastx.6                                                       | WUblastx.6                                                       | WUblastx.6                                                                  | HMMER<br>2.1.1<br>WUblastx.6<br>4                                                                            | HMMER<br>2.1.1<br>WUblastx.6<br>4                                                                             |                                                           | WUblastx.6                          |
|                   | 178                                                              | 336                                                              | 337                                                              | 179                                                                         | 180                                                                                                          | 338                                                                                                           | 181                                                       | 183                                 |
|                   | 1310821                                                          | 796807                                                           | 590738                                                           | 545534                                                                      | 1160395                                                                                                      | 853373                                                                                                        | 700627                                                    | 1041383                             |
|                   | HNTB126                                                          | HNTB126                                                          | HNTB126                                                          | HNTBL27                                                                     | HNTCE26                                                                                                      | HNTCE26                                                                                                       | HNTNC20                                                   | HNTSY18                             |

| 931 | 296 | 863 | 662 | 922 | 1276 | 1356 | 1517 | 1157 | 1201 | 892 | 584 | 1198 | 551 | 537 | 329 | 389 | 329 | 581 | 1523 | 1076 | 201                   | 1021               |                                | 1500                              | 815                                          | 1499                              | 737                         | 857                               | 877                 |
|-----|-----|-----|-----|-----|------|------|------|------|------|-----|-----|------|-----|-----|-----|-----|-----|-----|------|------|-----------------------|--------------------|--------------------------------|-----------------------------------|----------------------------------------------|-----------------------------------|-----------------------------|-----------------------------------|---------------------|
| 824 | 42  | 99  | 48  | 416 | 635  | 1078 | 1482 | 1101 | 539  | 530 | 228 | 755  | 8   | 379 | 15  | 66  | 54  | 99  | 1485 | 1017 | 326                   | 1119               |                                | 43                                | 288                                          | 42                                | 318                         | 72                                | 1584                |
| 762 | 28% | 30% | 36% | 30% | 73%  | 73%  | 41%  | 20%  | 78%  | 79% | 36% | 79%  | 78% | 33% | 32% | 34% | 30% | 25% | 45%  | 40%  | %19                   | 100%               |                                | %58                               | 189.8                                        | %58                               | 162.2                       | 81%                               | 81%                 |
|     |     |     |     |     |      |      |      |      |      |     |     |      |     |     |     |     |     |     |      |      | O9GMX5                | O9H1S5             |                                | MTN3_HUMAN                        | PF00092                                      | MTN3_HUMAN                        | PF00092                     | MTN3_HUMAN                        | MTN3_HUMAN          |
|     |     |     |     |     |      |      |      |      |      |     |     |      |     |     |     |     |     |     |      |      | (Q9GMX5) HYPOTHETICAL | (O9H1S5) BA110H4.2 | (SIMILAR TO MEMBRANE PROTEIN). | (O15232) MATRILIN-3<br>PRECURSOR. | PFAM: von Willebrand factor<br>type A domain | (O15232) MATRILIN-3<br>PRECURSOR. | PFAM: von Willebrand factor | (O15232) MATRILIN-3<br>PRECURSOR. | (015232) MATRILIN-3 |
|     |     |     |     |     |      |      |      |      |      |     |     |      |     |     |     |     |     |     |      |      | WUblastx.6            | WUblastx.6         | 4                              | WUblastx.6<br>4                   | HMMER<br>2.1.1                               | WUblastx.6                        | HMMER<br>2.1.1              | WUblastx.6                        | 'Ublastx.6          |
|     |     |     |     |     |      |      |      |      |      |     |     |      |     |     |     |     |     |     |      |      | 340                   | 186                |                                | 188                               | 341                                          |                                   | 342                         |                                   | 343                 |
|     |     |     |     |     |      |      |      |      |      |     |     |      |     |     |     |     |     |     |      |      | 056268                | 422913             |                                | 1184465                           | 968616                                       |                                   | 906694                      |                                   | 902639              |
|     |     |     |     |     |      |      |      |      |      |     |     |      |     |     |     |     |     |     |      |      | HNTSY18               | HODDN92            |                                | ноғмозз                           | НОЕМQ33                                      |                                   | ноғмозз                     |                                   | HOFMQ33             |

|            | 911                                        | 721                     | 2414                                  | 585<br>496                                 | 489              | 1029                    | 593<br>544                         | -351                                  | 3408                                                            | 908                                                | 757                                | 402<br>722<br>508                  | 934<br>890<br>122<br>872                          | 1415<br>256 | 256<br>256<br>256 |
|------------|--------------------------------------------|-------------------------|---------------------------------------|--------------------------------------------|------------------|-------------------------|------------------------------------|---------------------------------------|-----------------------------------------------------------------|----------------------------------------------------|------------------------------------|------------------------------------|---------------------------------------------------|-------------|-------------------|
|            | 937                                        | 170                     | 324                                   | 406                                        | 001              | 61                      | 468<br>143                         | -115                                  | 808                                                             | 498                                                | 128                                | 127<br>507<br>401                  | 617<br>633<br>24<br>570                           | 1317        | 137               |
|            | %66<br>%88                                 | 100%                    | 100%                                  | %96<br>%95                                 | 211.5            | 98%<br>49%              | %98<br>%98                         | 76.2                                  | %18                                                             | 48%                                                | 93%                                | 888%<br>95%<br>97%                 | 49%<br>33%<br>51%<br>35%                          | 33%<br>51%  | 34%               |
|            | Q8WUF2                                     | 595090                  | CAC37794                              | Q9BQI2                                     | PF00856          | 096028                  | 6A8G6O                             | PF01562                               | ATS1_MOUSE                                                      | Q96NR6                                             | £\$0260                            | (S)CO(S3                           | 060448                                            |             |                   |
| PRECURSOR. | (Q8WUF2) Hypothetical 23.7<br>kDa protein. | (O60565) GREMLIN (DRM). | (CAC37794) H-l(3)mbt-like<br>protein. | (Q9BQI2) HYPOTHETICAL<br>69.3 KDA PROTEIN. | PFAM: SET domain | (096028) WHSC1 PROTEIN. | (Q9D8Y9) 1810018L05RIK<br>PROTEIN. | PFAM: Reprolysin family<br>propeptide | (P97857) ADAM-TS 1<br>PRECURSOR (EC 3.4.24) (A<br>DISINTEGRIN A | (Q96NR6) CDNA FLJ30278<br>fis, clone BRACE2002755. | (Q9CQS3) 1110018M03RIK<br>PROTEIN. | (Q9CQS3) 1110018M03RIK<br>PROTEIN. | (060448) NEURONAL<br>THREAD PROTEIN AD7C-<br>NTP. |             |                   |
| 4          | WUblastx.6                                 | WUblastx.6              | WUblastx.6                            | WUblastx.6<br>4                            | HMMER<br>2.1.1   | WUblastx.6              | WUblastx.6                         | HMMER<br>2.1.1                        | WUblastx.6<br>4                                                 | WUblastx.6                                         | WUblastx.6                         | WUblastx.6<br>4                    | WUblastx.6                                        |             |                   |
|            | 344                                        | 189                     | 190                                   | 347                                        | 348              |                         | 192                                | 193                                   |                                                                 | 194                                                | 195                                | 350                                | 196                                               |             |                   |
|            | 702186                                     | 873264                  | 1352356                               | 858338                                     | 857453           |                         | 854234                             | 429229                                |                                                                 | 520202                                             | 1310868                            | 590741                             | 682699                                            |             |                   |
|            | НОҒМQ33                                    | HOHBY44                 | HOQBJ82                               | ноовля2                                    | ноовля2          |                         | HOSDJ25                            | HOUCQ17                               |                                                                 | HPEAD79                                            | HPIBO15                            | HPIBO15                            | HPJB133                                           |             |                   |

| 146<br>942 | 2508<br>338<br>2823                        | 348<br>992                  | 582<br>162                                                                  | 999                                                                         | 099                                                                         | 1312                                           | 1017                                          | 336                                          | 679<br>371<br>507                                     | 665<br>357<br>493                                     | 253             | 1581 253                                     | 1755                                                   |                      |
|------------|--------------------------------------------|-----------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------|----------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|-----------------|----------------------------------------------|--------------------------------------------------------|----------------------|
| 3886       | 1420<br>210<br>2701                        | 64<br>468                   | 346<br>16                                                                   | 163                                                                         | 157                                                                         | 62                                             | 70<br>490                                     | 124                                          | 647<br>144<br>247                                     | 633<br>130<br>233                                     | 1452            | 1649                                         | 1468                                                   |                      |
| 50%<br>47% | 97%<br>27%<br>75%                          | %69<br>%19                  | 94%<br>81%                                                                  | 100%                                                                        | 100%                                                                        | %66                                            | 83%                                           | %56                                          | 63%<br>48%<br>93%                                     | 63%<br>48%<br>92%                                     | %86             | 82%<br>98%                                   | %66<br>%86                                             |                      |
|            | Q9GKV3                                     | O9VWN8                      | Q9H8F3                                                                      | Q9NP77                                                                      | Q9NP77                                                                      | pir T08724 T08724                              | AAH08720                                      | Q91XD7                                       | 09НА75                                                | Q9HA75                                                | AAH08084        | AAH08084                                     | Q9Y5X6                                                 |                      |
|            | (Q9GKV3) HYPOTHETICAL<br>41.8 KDA PROTEIN. | (Q9VWN8) CG7307<br>PROTEIN. | (Q9H8F3) CDNA FLJ13680<br>FIS, CLONE PLACE2000007,<br>HIGHLY SIMILAR TO HOM | (Q9NP77) CDNA FLJ10947<br>FIS, CLONE PLACE1000066,<br>WEAKLY SIMILAR TO SSU | (Q9NP77) CDNA FLJ10947<br>FIS, CLONE PLACE1000066,<br>WEAKLY SIMILAR TO SSU | hypothetical protein<br>DKFZp566D213.1 - human | (AAH08720) Unknown<br>(protein for MGC:8447). | (Q91XD7) Unknown (protein<br>for MGC:18896). | (Q9HA75) CDNA FLJ12122<br>FIS, CLONE<br>MAMMA1000129. | (Q9HA75) CDNA FLJ12122<br>FIS, CLONE<br>MAMMA1000129. |                 | (AAH08084) Hypothetical 50.4<br>kDa protein. | (Q9Y5X6) BLOOD PLASMA<br>GLUTAMATE<br>CARROXYPEPTIDASE | PRECURSOR (EC 3.4.17 |
|            | WUblastx.6<br>4                            | WUblastx.6                  | WUblastx.6<br>4                                                             | WUblastx.6<br>4                                                             | WUblastx.6<br>4                                                             | WUblastx.6<br>4                                | WUblastx.6<br>4                               | WUblastx.6                                   | WUblastx.6<br>4                                       | WUblastx.6<br>4                                       | WUblastx.6<br>4 | WUblastx.6                                   | WUblastx.6<br>4                                        |                      |
|            | 198                                        | 354                         | 355                                                                         | 199                                                                         | 356                                                                         | 200                                            | 357                                           | 358                                          | 201                                                   | 359                                                   | 202             | 360                                          | 203                                                    |                      |
|            | 1146674                                    | 1034817                     | 1046434                                                                     | 846357                                                                      | 639118                                                                      | 1352342                                        | 844216                                        | 484735                                       | 882176                                                | 588460                                                | 871221          | 706332                                       | 877666                                                 |                      |
|            | HPJCL22                                    | HPJCL22                     | HPJCL22                                                                     | HPMDK28                                                                     | HPMDK28                                                                     | HPRAL78                                        | HPRAL78                                       | HPRAL78                                      | HRABA80                                               | HRABA80                                               | HRACD15         | HRACD15                                      | HRACJ35                                                |                      |

|                                                                                  | 361 WUblastx.6 ( | OD PLASMA                                               | 9X5X6Q  | %86  | 1435 | 1722 |
|----------------------------------------------------------------------------------|------------------|---------------------------------------------------------|---------|------|------|------|
| 4                                                                                | <u> </u>         | GLUTAMATE<br>CARBOXYPEPTIDASE<br>PRECTIRSOR GEC 3.4.17  |         | %66  | 66   | 1439 |
| 362 WUblastx.6                                                                   | ٦٠               | (Q9Y646)                                                | Q9Y646  | %96  | 202  | 785  |
| 1                                                                                | ٩.               | AMINOPEPTIDASE.                                         |         | 100% | -    | 519  |
| 204 HMMER<br>2.1.1                                                               | <u> </u>         | PFAM: Immunoglobulin<br>domain                          | PF00047 | 32   | 282  | 755  |
| WUblastx.6                                                                       |                  | (Q8WXH3) FREB.                                          | Q8WXH3  | %18  | 6    | 1085 |
| 363 WUblastx.6 (                                                                 |                  | (Q8WXH3) FREB.                                          | Q8WXH3  | %46  | 15   | 969  |
| 4                                                                                |                  |                                                         |         | 100% | 547  | 588  |
| 364 WUblastx.6 ((                                                                |                  | (Q9EPP8) VIRION-                                        | Q9EPP8  | %96  | 118  | 35   |
| AS<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH<br>SH | 多黑宝              | ASSOCIATED NUCLEAR-<br>SHUTTLING PROTEIN<br>(FRAGMENT). |         |      |      |      |
| 365 WUblastx.6 (Q                                                                | o                | (Q8WXH3) FREB.                                          | Q8WXH3  | %56  | 489  | 869  |
| 4                                                                                |                  | -                                                       |         | 29%  | en ( | 341  |
|                                                                                  | J                |                                                         |         | 9/9/ | 66   | 480  |
| 205 WUblastx.6 (Q9                                                               | Ö,51             | (Q96ES0) Unknown (protein<br>for MGC:16944).            | Q96ES0  | %96  | 7    | 1146 |
| 366 WUblastx.6 (C                                                                | 0,0              | (Q96ES0) Unknown (protein<br>for MGC:16944).            | 09ES0   | %66  | 10   | 762  |
| 367 WUblastx.6 (Q                                                                | O,5              | (Q96ES0) Unknown (protein<br>for MGC:16944).            | 08E80   | %56  | 7    | 1056 |
| 206 WUblastx.6 (Q                                                                | IO.              | (Q9H728) CDNA: FLJ21463                                 | Q9H728  | %99  | 418  | 576  |
| 4                                                                                | ۴I               | IS, CLONE COL04765.                                     |         | 78%  | 281  | 748  |
| 207 WUblastx.6 (Q                                                                | O ∺              | (Q9NX85) CDNA FLJ20378<br>FIS, CLONE KAIA0536.          | Q9NX85  | %19  | 196  | 674  |
| 208 WUblastx,6 (C                                                                | - C              | (Q9Y279) Z39IG PROTEIN PRECURSOR.                       | Q9Y279  | 100% | 09   | 1256 |
| 369 HMMER P                                                                      |                  | PFAM: Immunoglobulin<br>domain                          | PF00047 | 18.7 | 225  | 470  |
| WUblastx.6 ((                                                                    |                  | (Q9Y279) Z39IG PROTEIN                                  | Q9Y279  | %88  | 444  | 1040 |
| 1 14 FR                                                                          | ÷Ι               | ECUKSOR.                                                |         | 9270 | 170  | 246  |

| 797                           | 281             | 702             | 298             | 966                                             | 286                                      | 734            | 1037                                     | 286              | 3635            | 1789                       | 1789       | 1791 | 1790 | 1670                         | 1126                             | 1311                             | 730<br>579        | 536 |
|-------------------------------|-----------------|-----------------|-----------------|-------------------------------------------------|------------------------------------------|----------------|------------------------------------------|------------------|-----------------|----------------------------|------------|------|------|------------------------------|----------------------------------|----------------------------------|-------------------|-----|
| 66                            | 99              | 4               | v.              | 1289                                            | 38                                       | 999            | 54                                       | 32               | 786             | 1091                       | 1715       | 127  | 1716 | 9                            | 146                              | 436                              | 825<br>623        | 730 |
| %66                           | 100%            | %66             | %66             | 74%                                             | %96                                      | 23.4           | %66                                      | %16              | 83%             | %09                        | 60%<br>52% | 73%  | 32%  | 93%                          | %89                              | %99                              | 62%               | 26% |
| Q9BYJ0                        | O9BYJ0          | Q9BZW5          | Q9NV22          | О9Н728                                          | Q96D15                                   | PF00036        | Q96D15                                   | Q96D15           | BAB85613        | BAB85613                   |            |      |      | BAB85613                     | Q9CZY7                           | Q9CZY7                           | Q9P195            |     |
| WUblastx.6 (Q9BYJ0) KSP37. (0 | (Q9BYJ0) KSP37. | 1.              | 10              | (Q9H728) CDNA: FLJ21463<br>FIS, CLONE COL04765. | (Q96D15) Hypothetical 37.5 (Aba protein. | and            | (Q96D15) Hypothetical 37.5 (ADa protein. | ypothetical 37.5 | (BAB85613) URB. | WUblastx.6 (BAB85613) URB. |            |      |      | WUblastx.6 (BAB85613) URB. 1 | (Q9CZY7) 2610307008RIK (PROTEIN. | (Q9CZY7) 2610307O08RIK (PROTEIN. | (Q9P195) PRO1722. |     |
| WUblastx.6<br>4               | WUblastx.6<br>4 | WUblastx.6<br>4 | WUblastx.6<br>4 | WUblastx.6<br>4                                 | WUblastx.6<br>4                          | HMMER<br>2.1.1 | WUblastx.6<br>4                          | WUblastx.6<br>4  | WUblastx.6<br>4 | WUblastx.6                 | 4          |      |      | WUblastx.6                   | WUblastx.6                       | WUblastx.6                       | WUblastx.6<br>4   |     |
| 209                           | 370             | 210             | 213             | 214                                             | 215                                      | 372            |                                          | 373              | 216             | 374                        |            |      |      | 375                          | 217                              | 376                              | 219               |     |
| 834619                        | 1/0988          | 795252          | 612823          | 289447                                          | 1304677                                  | 869199         |                                          | 371784           | 1352409         | 1074734                    |            |      |      | 872570                       | 676075                           | 409905                           | 467397            |     |
| HSDFJ26                       | HSDFJ26         | HSDJA15         | HSHAX21         | HSIDJ81                                         | HSJBQ79                                  | HSJBQ79        |                                          | HSJBQ79          | HSKDA27         | HSKDA27                    |            |      |      | HSKDA27                      | HSKGN81                          | HSKGN81                          | HSNAD72           |     |

| HSUBW09 | 413246  | 223 | WUblastx.6      | (Q95LL0) Hypothetical 11.3                           | 07T56O            | 73%  | 685  | 633  |
|---------|---------|-----|-----------------|------------------------------------------------------|-------------------|------|------|------|
|         |         |     | 4               | kDa protein.                                         |                   | 77%  | 327  | 611  |
| HSVBU91 | 898965  | 224 | WUblastx.6      | cytoplasmic linker protein<br>CLIP-115 - rat         | pir T42734 T42734 | %58  | 356  | 171  |
| HSXGI47 | 886200  | 225 | WUblastx.6      | (Q9H728) CDNA: FLJ21463                              | Q9H728            | %95  | 585  | 986  |
|         |         |     | 4               | FIS, CLONE COL04/65.                                 |                   | 92%  | 79/  | 696  |
| HSYAZ63 | 1177537 | 226 | WUblastx.6      | (Q9Y613) FH1/FH2                                     | FHOS_HUMAN        | %86  | 688  | 1713 |
|         |         |     | 4               | DOMAINS-CONTAINING                                   |                   | 25%  | 272  | 544  |
|         |         |     |                 | PROTEIN (FORMIN                                      |                   | 81%  | 2101 | 2514 |
|         |         |     |                 | HOMOLOG                                              |                   | 100% | 478  | 750  |
|         |         |     |                 |                                                      |                   | 95%  | 3007 | 3090 |
|         |         |     |                 |                                                      |                   | 78%  | 586  | 654  |
|         |         |     |                 |                                                      |                   | 45%  | 809  | 670  |
|         |         |     |                 |                                                      |                   | 78%  | 1015 | 1458 |
|         |         |     |                 |                                                      |                   | 33%  | 2030 | 2119 |
|         |         |     |                 |                                                      |                   | %95  | 2005 | 2052 |
|         |         |     |                 |                                                      |                   | 73%  | 2573 | 2941 |
| HSYAZ63 | 862063  | 378 | WUblastx.6      | (Q9Y613) FH1/FH2                                     | FHOS HUMAN        | %69  | 458  | 871  |
|         |         |     | 4               | DOMAINS-CONTAINING                                   |                   | 65%  | 1364 | 1447 |
|         |         |     |                 | PROTEIN (FORMIN                                      |                   | 73%  | 930  | 1298 |
|         |         |     |                 | HOMOLOG                                              |                   | 25%  | 362  | 418  |
|         |         |     |                 |                                                      |                   | 33%  | 387  | 476  |
|         |         |     |                 |                                                      |                   | 100% | 14   | 70   |
| HSYBG37 | 1056317 | 227 | WUblastx.6<br>4 | hypothetical protein c316G12.3<br>[imported] - human | pir T45062 T45062 | 100% | 47   | 961  |
| HSYBG37 | 581098  | 379 | WUblastx.6      | hypothetical protein c316G12.3<br>finported1 - human | pir T45062 T45062 | 100% | 48   | 962  |
| HTADW91 | 844835  | 228 | WUblastx.6      | (Q8WV10) Hypothetical 38.4<br>kDa protein.           | Q8WV10            | %98  | 155  | 1117 |
| HTAEE28 | 1018291 | 229 | WUblastx.6      | (Q9D412) 4932408F18RIK<br>PROTEIN,                   | Q9D4I2            | 78%  | 319  | 1161 |
| HTAEE28 | 882919  | 380 | WUblastx.6      | (Q9D412) 4932408F18RIK<br>PROTEIN.                   | Q9D4I2            | 78%  | 372  | 617  |
| HTAEE28 | 864120  | 381 | WUblastx.6<br>4 | (Q9D412) 4932408F18RIK<br>PROTEIN.                   | Q9D412            | 76%  | 142  | 768  |
| HTDAF28 | 396835  | 230 | WUblastx.6      | (Q9BX79) STRA6 ISOFORM                               | Q9BX79            | %86  | 17   | 298  |

|         |     | 4               |                                                            |            |             |            |            |
|---------|-----|-----------------|------------------------------------------------------------|------------|-------------|------------|------------|
| 206980  | 232 | HMMER<br>2.1.1  | PFAM: Immunoglobulin<br>domain                             | PF00047    | 48.5        | 200        | 706        |
|         |     | WUblastx.6      | (AAG49022) Junctional<br>adhesion molecule 2.              | AAG49022   | %66         | 65         | 952        |
| 1352272 | 235 | WUblastx.6<br>4 | (Q9BWYI) BASS2MI1.5<br>(NOVEL PROTEIN)<br>(FRAGMENT).      | Q9BWY1     | 100%        | 158<br>351 | 193<br>779 |
| 658744  | 384 | WUblastx.6      | (Q9DAR9) 1700001D09RIK<br>PROTEIN.                         | Q9DAR9     | %09<br>**LL | 525<br>163 | 743        |
| 381941  | 385 | WUblastx.6      | (Q9НВК8) АD026.                                            | О9НВК8     | 92%         | 191        | 229<br>633 |
| 836072  | 236 | WUblastx.6      | (AAH24188) Similar to RIKEN AAH24188 cDNA 4930453N24 gene. | AAH24188   | 100%        | 22         | 465        |
| 847090  | 237 | WUblastx.6<br>4 | (Q9JI83) EPCS26 (PLAC1) (PLACENTAL SPECIFIC PROTEIN 1).    | Q9J183     | 34%         | 33         | 395        |
| 634852  | 238 | WUblastx.6      | (Q8WTZ3) Hypothetical 27.2<br>kDa protein.                 | Q8WTZ3     | %89<br>%99  | 543<br>806 | 499<br>534 |
| 854941  | 240 | WUblastx.6      | (095880) UNKNOWN.                                          | 095880     | 100%        | 2191       | 2577       |
| 566683  | 386 | WUblastx.6      | (095880) UNKNOWN.                                          | 095880     | 100%        | 356        | 742        |
| 916616  | 241 | HMMER<br>2.1.1  | PFAM: PMP-<br>22/EMP/MP20/Claudin family                   | PF00822    | 81.5        | 127        | 099        |
|         |     | WUblastx.6      | (P57739) CLAUDIN-2.                                        | CLD2_HUMAN | 100%        | 118        | 807        |
| 895024  | 387 | HMMER<br>2.1.1  | PFAM: PMP-<br>22/EMP/MP20/Claudin family                   | PF00822    | 55.9        | 120        | 200        |
|         |     | WUblastx.6      | (P57739) CLAUDIN-2.                                        | CLD2_HUMAN | %86         | 111        | 530        |
| 880868  | 388 | WUblastx.6      | (P57739) CLAUDIN-2.                                        | CLD2_HUMAN | %96         | 96         | 353        |
| 1008159 | 244 | WUblastx.6<br>4 | (O00172) LINE-1 REVERSE<br>TRANSCRIPTASE<br>(FRAGMENT).    | O00172     | %05         | 932        | 714        |

| HTXAJ12 | 1310814 | 246 | WUblastx.6  | ) 2210021G21RIK               | Q9D7W4            | 45%   | 12   | 77   |
|---------|---------|-----|-------------|-------------------------------|-------------------|-------|------|------|
|         |         |     |             | PROTEIN.                      |                   | 21%   | 6    | 273  |
| HTXAJ12 | 567434  | 391 | Ublastx.6   | (AAH24685) Similar to         | AAH24685          | %001  | 6    | 95   |
|         |         |     | 4           | transmembrane 4 superfamily   |                   | %86   | 97   | 267  |
| HTX1M03 | 603918  | 247 | WTiblastx 6 | (O9BRH0) SIMILAR TO           | O9BRH0            | %001  | 470  | 595  |
|         |         | _   |             | DKFZP727C091 PROTEIN.         |                   | %66   | 564  | 1760 |
| HTXKF95 | 891275  | 248 | WUblastx.6  | (AAH08360) Similar to         | AAH08360          | 84%   | 324  | 644  |
|         |         |     | 4           | hypothetical protein FLJ22376 |                   | 95%   | 81   | 203  |
| HTXKF95 | 834438  | 392 | WUblastx.6  | (AAH08360) Similar to         | AAH08360          | %001  | 2    | 553  |
|         |         |     | 4           | hypothetical protein FLJ22376 |                   |       |      |      |
| HTXON32 | 838288  | 249 | WUblastx.6  | (Q96NR6) CDNA FLJ30278        | O96NR6            | %85   | 1397 | 1498 |
|         |         |     | 4           | fis, clone BRACE2002755.      |                   | 94%   | 1194 | 1397 |
| HWAAD63 | 838626  | 252 | HMMER       | PFAM: Sodium/calcium          | PF01699           | 62.8  | 346  | 453  |
|         |         |     | 2.1.1       | exchanger protein             |                   |       |      |      |
|         |         |     | WUblastx.6  | (Q9HC58)                      | Q9HC58            | %59   | 229  | 813  |
|         |         |     | 4           | SODIUM/CALCIUM                |                   |       |      |      |
|         |         |     |             | EXCHANGER NCKX3.              |                   |       |      |      |
| HWAAD63 | 833089  | 393 | HMMER       | PFAM: Sodium/calcium          | PF01699           | 37.8  | 346  | 453  |
|         |         |     | 2.1.1       | exchanger protein             |                   |       |      |      |
|         |         |     | WUblastx.6  | (Q9HC58)                      | Q9HC58            | %84   | 229  | 453  |
|         |         |     | 4           | SODIUM/CALCIUM                |                   | %55   | 459  | 969  |
|         |         |     |             | EXCHANGER NCKX3.              |                   | 72%   | 533  | 814  |
| HWAAD63 | 793875  | 394 | HMMER       | PFAM: Sodium/calcium          | PF01699           | 113.7 | 336  | 773  |
|         |         |     | 2.1.1       | exchanger protein             |                   |       |      |      |
|         |         |     | WUblastx.6  | (Q9HC58)                      | Q9HC58            | %9L   | 219  | 908  |
|         |         |     | 4           | SODIUM/CALCIUM                |                   |       |      |      |
|         |         |     |             | EXCHANGER NCKX3.              |                   |       |      |      |
| HWBCP79 | 846382  | 254 | WUblastx.6  | (Q96MM0) CDNA FLJ32172        | 0MM96O            | 72/%  | 340  | 143  |
|         |         |     | 4           | fis, clone PLACE6000555.      |                   | %58   | 158  | 78   |
| HWBCP79 | 646977  | 395 | WUblastx.6  | (Q96MM0) CDNA FLJ32172        | 0ММ96О            | 27%   | 330  | 133  |
|         |         |     | 4           | fis, clone PLACE6000555.      |                   | %58   | 148  | 89   |
| HWBEM18 | 949402  | 255 | WUblastx.6  | nuclear pore protein gp210    | pirIS04921 S04921 | 84%   | 102  | 5735 |
|         |         |     | 4           | precursor - rat               |                   |       |      |      |
| HWBEM18 | 906580  | 396 | WUblastx.6  | nuclear pore protein gp210    | pir S04921 S04921 | 82%   | 92   | 2629 |
|         |         |     | 4           | precursor - rat               |                   | 30%   | 2595 | 2732 |

| HSDEZ20   704101   404   WUblasx.6   probable voltage-activated   prir T17101 T17101   89% 9   9 |        |     |            |                     |               |     |   |     |
|--------------------------------------------------------------------------------------------------|--------|-----|------------|---------------------|---------------|-----|---|-----|
| on channel - rat                                                                                 | 704101 | 404 | WUblastx.6 | ble voltage-actival | Ir T17101 T17 | %68 | 6 | 335 |
|                                                                                                  |        |     | 4          | on channel - r      |               |     |   |     |

## RACE Protocol For Recovery of Full-Length Genes

[0118] Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., Proc. Nat'l, Acad. Sci. USA, 85;8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start codon of translation, therefor. The following briefly describes a modification of this original 5' RACE procedure. Poly A+ or total RNA is reverse transcribed with SUPERSCRIPT™ II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, SalI and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or SalI, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar methods known in the art and/or commercial kits are used to amplify and recover 3' ends. 101191 Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-stranded cDNA), developed by Dumas et al., Nucleic Acids Res., 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to the first-

difficult to sequence past.

[0120] An alternative to generating 5° or 3° cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is

[0121] RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes

[0122] Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3' RACE. While the full length gene may be present in the library and can be identified by probing, a useful method for generating the 5' or 3' end is to use the existing sequence information from

the original cDNA to generate the missing information. A method similar to 5' RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript and a primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase if used is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant gene.

The present invention also relates to vectors or plasmids which include such DNA sequences, as [0123] well as the use of the DNA sequences. The material deposited with the ATCC™ (e.g., as described in columns 2 and 3 of Table 1A, and/or as set forth in Table 1B. Table 6, or Table 7) is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as described, for example, in Table 1A and Table 7. These deposits are referred to as "the deposits" herein. The tissues from which some of the clones were derived are listed in Table 7, and the vector in which the corresponding cDNA is contained is also indicated in Table 7. The deposited material includes cDNA clones corresponding to SEQ ID NO:X described, for example, in Table 1A and/or Table 1B (ATCC™ Deposit No:Z). A clone which is isolatable from the ATCCTM Deposits by use of a sequence listed as SEQ ID NO:X, may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Furthermore, although the sequence listing may in some instances list only a portion of the DNA sequence in a clone included in the ATCCTM Deposits, it is well within the ability of one skilled in the art to sequence the DNA included in a clone contained in the ATCCTM Deposits by use of a sequence (or portion thereof) described in, for example Tables 1A and/or Table 1B or Table 2, by procedures hereinafter further described, and others apparent to those skilled in the art

[0124] Also provided in Table 1A and Table 7 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

[0125] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), Pilluescript (pBS) (Short, J. M., et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic

Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into E. coli strain XL-1 Blue, also available from Stratagene.

[0126] Vectors pSportl, p.CMVSport 1.0, p.CMVSport 2.0 and p.CMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Guithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., Focus 15:59-(1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR\*2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).

10127] The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the deposited clone (ATCCTM Deposit No:Z). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material

10128] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. 
Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, fulllength coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X or the 
complement thereof, polypeptides encoded by genes corresponding to SEQ ID NO:X or the complement 
thereof, and/or the cDNA contained in ATCC™ Deposit No:Z, using information from the sequences 
disclosed herein or the clones deposited with the ATCC™ For example, allelic variants and/or species 
homologs may be isolated and identified by making suitable probes or primers from the sequences provided 
herein and screening a suitable mucleic acid source for allelic variants and/or the desired homologue.

(0129) The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

[0130] The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[0131] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

In 132 The present invention provides a polymuclotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA sequence contained in ATCC<sup>™</sup>Deposit No:Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or a complement thereof, a polypeptide encoded by the cDNA contained in ATCC<sup>™</sup>Deposit No:Z, and/or the polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table IC. Polynucleotides encoding a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA contained in ATCC<sup>™</sup>Deposit No:Z, and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA contained in ATCC<sup>™</sup>Deposit No:Z, and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table IC are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, a nucleic acid sequence encoding a polypeptide encoded by the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA contained in ATCC<sup>™</sup>Deposit No:Z.

Moreover, representative examples of polynucleotides of the invention comprise, or 101331 alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in Table 1C column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in Table 1C column 6. or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column Polypeptides encoded by these polypucleotides, other polypucleotides that encode these polypeptides. and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

10134] Further, representative examples of polymucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), or any combination thereof. Additional, representative examples of polymucleotides of the invention comprise, or alternatively

consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the abovedescribed polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polyneptides are also encompassed by the invention.

[0135] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEO ID NO:B (see Table 1C, column 5), In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEO ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (See Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[0136] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of Table 1C column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1C column 6, or any combination thereof. In preferred embodiments, the polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1C column 6, wherein sequentially delineated sequences in the table (i.e. corresponding to those exons located closest to each other) are directly contiguous in a 5' to 3' orientation. In further embodiments, above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEO ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of. sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0137] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO.X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

10138 In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table IC which correspond to the same Clone ID (see Table IC, column I), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table IA, Table IB, or Table IC) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same Clone ID. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO.X (e.g., as defined in Table 1A, Table 1B, or Table 1C) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO.X correspond to the same row of column 6 of

Table 1C. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3° 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5° 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In additional specific embodiments, polymucleotides of the invention comprise, or alternatively consist of, a polymucleotide sequence in which the 3° 10 polymucleotides of one of the sequences delineating in column 6 of Table 1C and the 5° 10 polymucleotides of a fragment or variant of the sequence of SEQ ID NO:X are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polymucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polymucleotides and/or nucleic acids, other polymucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embediments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3° 10 polynucleotides of the sequence of SEQ ID NO.X and the 5° 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polyneptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embediments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3° 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5° 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 10 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids, other polynucleotides and/or mucleic acids, other polynucleotides and/or mucleic acids, and polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides, are also encompassed by the invention.

[10144] In further specific embodiments, polynucleotides of the invention comprise, or alternatively

[0144] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringer, conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3° 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5° 10 polynucleotides of another sequence in column 6 corresponding to the same Clone 10 (see Table 1C, column 1) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embediments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one sequence in column 6 corresponding to the same contig sequence identifer SEQ ID NO:X (see Table 1C, column 2) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3<sup>1</sup> 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5<sup>1</sup> 10 polynucleotides of another sequence in column 6 corresponding to the same row are directly contiguous. In preferred embodiments, the 3<sup>1</sup> 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5<sup>1</sup> 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

Table 3: Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the

present invention. Accordingly, for each contig sequence (SEO ID NO:X) listed in the fifth column of Table 1A and/or the fourth column of Table 1B, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. More specifically, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a and b are integers as defined in columns 4 and 5, respectively, of Table 3. In specific embodiments, the polynucleotides of the invention do not consist of at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. as disclosed in column 6 of Table 3 (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone). In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

|         |           | Accession Numbers                         | HEGG1316, RE720453, AW867199, AW68780-BHR9571, BRG015589, BRG01518, BRT91481, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR954, AW8710-BHR952, AW8 | AU09013, AU76772, BG116691, AT79075, BE758376, A0880172, AR81570, BE671143, A15923-6, AV700244, A159294, BEZ461613, AA84681, AVX004400, A1890251, BE761656, T79244, BF44561, AA400720, AA30024, AA472790, AA30217, AA322321, AA406651, A186923, BF866652, A126291, AA406246, AA300245, AW072158, T79197, AA417721, AV882333, F34003, A11260629, A1262951, A4498669, AA300245, AW072158, T79197, AA417721, AV882333, F34003, A112606, A126024, A1260 | A112664, A210666, A710782, B1875227, NURA, AW95611, I 10182, B182121, A31899, A70665, A710266, A710725, A712466, A7091668, A7091668, A7091668, A7091668, A7091668, A7091668, A7091668, A709167, A709166, A709167, A709169, A7071661, A709169, A709169, A709161, A709169, |
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|         |           | EST Disclaimer<br>Range of a   Range of b | 15 - 2703                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 15 - 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|         |           | EST Di<br>Range of a                      | 1 - 2689                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 - 746                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1 - 1431                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|         |           | Contig<br>ID:                             | 884134                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| Table 5 |           | DNA Clone                                 | H2CBU83                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| AD68514, AV710030, AV70029, E3590, IR216659, E3350, BH467615, AV738516, BES08802, AV736394, BG110890, AV742814, AV710954, BG10890, AV742814, AV710954, BF003801, T0066, R00459, F33392, BR02958, BF003823, AV746731, BE73842, BF218458, AV777766, BF003803, BF003823, AV7401628, BF21913, BF274867, BF003257, AV441028, BF219131, BF274867, AR401028, BF219131, BF274867, BF27867, AV441028, BF219131, BF27402, BF27820, AV712969, BF21932, AV740167, F3023, AV740167, F3023, AV740167, F3023, AV740167, F3023, AV740167, F3023, AV74644, BF214457, BF214457, AV86535, BF278040, AV57545, BF214407, BF214457, AV86515, BF214457, AV86516, BF21509, D19917, BF210457, AV86514, BF21509, D19917, BF210754, AV86514, BF21509, D19917, BF210754, AV86514, BF21695, BF210754, B | AGESSEGA BESTORO, BESSORO, ANDRORS AN RESTORA, AT 1998 PT A ASSEGS, BRG54790, AUGSSEGS, BRG54790, AUGSSEGS, BRG54790, AUGSSEGS, BRC54790, AUGSSEGS, BRC54790, AUGSSEGS, BRC54790, AUGSSEGS, BRC5475, AVGSSEGS, AVGSSEGS, BESSEGS, BESSEGS, AUGSSEGS, BESSEGS, AUGSSEGS, BESSEGS, AUGSSEGS, BESSEGS, AUGSSEGS, BESTORO, AGESTOFO, ANDROGS, AUGSSEGS, BESTORO, AUGSSEGS, AUGSSEGS, AUGSSEGS, AUGSSEGS, BRC5470, AUGSSEGS, AUGSSEG, AUGSSEG, AUGSSEG, AUGSSEG, AUGSSEGS, AUGSSEGS, AUGSSEGS, AU | HEI 1995, BFI 1996, WNOTSIAR, ARMORIOT, A.ALSHOST, A.ASHASH, TRESSE, TSAGE, TSSEI, TERRIS, TSGEON, TSOOT, Z-G-EZ-T, ALTZ-CSO, BENGASH, BRESHOG, A.ASHAGH, BOOTIS GE BESHSKEI, BERSHOG, A.ASHAGH, BOOTIS GE BESHSKEI, BERSHOG, A.ASHAGH, BOOTIS GE BESHSKEI, BERSHOG, A.BSHAGH, BESHSTEI, A.BSHASH, BESHSTEI, BENGASTA, BENGASTA, BENGASTA, BENGASTA, BENGASTA, BENGASTA, BENGASTA, A.BSHASH, B.BSHASH, A.BSHASH, A.BSH |
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1722                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 15 - 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1708                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1-1319                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| A1343091, A1345677, BE966011, BE965621, A1340519, AW162189, BF814357, AW198144, A1446809,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| AV 11725, AV 110015, AV 062144, AL200952, AA000113, AV 062093, BESG4001, AA7 09155, BESG3918, BESG40051, AW023338, AV738730, BE873776, BG027082, BF032404, BG164035,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| BE613727, BG032219, AI863357, BF965884, AL048323, BG153050, AI636719, AV756658,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AW827289, AL048340, BE879905, BG109270, AW020693, AI686576, AW858254, BE964073, AL740703, AW827300, AW058233, AL048866, BC107825, AT00257, BC260037, AW824325, AL7407878, AR7407878, AW824325, AR7407878, AW824878, AW82 |
| BE047952, BF793031, AA643235, AI418254, AI623905, AI538764, AI524654, AI249946, BE964006,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AA848053, AV733819, AA635382, H42825, AI929108, BF924884, BG029053, BE974031, AI473451,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AV711509, BG252714, AL048644, BF868927, AL040241, BE883391, BF968622, AW068845,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| A1624293, BF813196, AW022494, BF340523, AL046463, AW020288, A1521596, AW021373, AW1221304, BF8016314, BF801643                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| A W 1621/94, BF915316, BF925370, BF686214, AB925980, BE963461, AB668204, AL242750, BE691942, BE735380, BF909758, AA579232, BG166687, AV715354, BE964767, AV756247, AV758825.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| BF814449, AL038445, BE965121, AW163834, BF343521, AW084056, BG032169, BE904851,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BF868811, BG104782, AI537677, BG122101, AI628325, AI590645, BE875402, AW083804, AI561299,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| BE908335, AW059828, BF753056, AI559863, AV726125, BF750879, AW265004, F26535, AI583032,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| BF811808, A1366974, A1355765, BF822127, A1609593, A1887775, A1858865, A1500061, BG121959,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AA572758, BF699668, AI348897, BE778024, BF814504, AI345224, AI357599, AV681949, T99953,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| A1589428, BG113851, BG110517, AL530922, AF169301.1, AC091736.1, AL442082.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| AB049853.1, AL389935.1, BC007364.1, S78214.1, X99717.1, AL122121.1, AK027161.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BC006195.1, BC001418.2, BC005858.1, AK000310.1, S77771.1, AL389939.1, AF090900.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| AL136789.1, BC004874.1, AL122045.1, AK026506.1, AL389978.1, AL049464.1, AF067420.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC007355.1, M86826.1, AB063071.1, AL110196.1, BC001293.1, BC007998.1, BC006287.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL096751.1, AL133565.1, AF057300.1, AF057299.1, Y10080.1, BC008387.1, AK026518.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL133081.1, AL162006.1, U42031.1, AK027142.1, U51587.1, AF177336.1, AK000137.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AL157479.1, AL1375471, AL33093.1, AB063008.1, AK025431.1, AL390167.1, BC008673.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| BC0003171, AB047869.1, AF205861.1, BC003650.1, AL135560.1, AR024538.1, BC000799.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AKUZG4801, AFZ180141, AL045821, AKUZ/1821, AKU04211, AKU042131, SASONS1, DOMITMA A ADMINISTRATION ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION AND ADMINISTRATION ADMINISTRATION ADMINISTRATION ADMINISTRATION AND ADMINISTRATION AND ADM |
| DCMVITTH-11, ADVISTOR   ADVISTOR   ALLEGASE)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| ABOGO912 AL1221111 ABOGO863 BC00513, ABOGO8091 ABO620911 A143141                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| AK026927.1, AL096744.1, AL137658.1, AL137705.1, AL137292.1, BC000778.1, BC008185.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| S61953.1, AL137283.1, AF097996.1, AL049430.1, AL390154.1, BC006164.1, AL512718.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL049314.1, J05032.1, AL117583.1, AB063046.1, AF110640.1, BC001349.1, AF120268.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AK000212.1, AK000083.1, BC006180.1, AK027164.1, AB047801.1, BC007534.1, BC000556.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC004905.1, AL110224.1, BC007021.1, AK026462.1, AL356278.8, AF162270.1, AL050277.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC008070.1, AL512684.1, AB047966.1, BC006408.1, AF225424.1, AK000655.1, AB060856.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| R94240, W33199, A1973178, A1891085, A1095849, BG059067, AL041411, A1358417, A1734140, A W. 233702 B FIGTS R3 D D D D S N N N N N N N N N N N N N N N                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| AA136576, BF875698, AL047920, A1290861, A1651363, A1917243, AA825161, BF594091, A1453790,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC008496.5, AL390035.10, AJ229041.1, AP001724.1, AL163267.2, AL121767.6, AC016759.11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| A.1590838.26, AC007671.7, AZ109799, AP001683.1, AC0246574, AC008007.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| AC007085, AF002026,1, AC009225,15, AL449104,5, AC016925,15, AL554915,11, AC078843,2, AL135926,12, AC0024491, AL450340,13, AL022401,1, AC012000,3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL391986.12, AL078591.18, AC009320.7, AC013448.7, AC007321.2, AL034369.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC012081.16, AL121823.12, AC002300.1, AL590404.5, AC040171.3, AC005610.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL445306.7, AL359914.14, AL031319.5, AL353684.8, AL162759.4, AL049565.3, AC001231.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC008170.2, AL031183.4, AC016568.4, AL451049.11, AL049588.11, AP001729.1, AC010142.4, AC062861.3 AE003080.3 AE003080.3 AE16230.3 AE16208.3 AE003080.3 AE00 |
| AL485468,8, AC0186454, AL355593.21, AL15986.21, AL358341.3, AL136147.10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AC079147.5, Z84487.2, AL132821.17, AC022710.10, AC073348.8, AC006206.3, AL365204.11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL445465.10, AC005243.1, AC067945.4, AL589786.8, AC012323.7, AL132715.3, AJ225782.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC090043.1, AC079905.28, AF274857.1, AC004066.1, AL355294.14, AC010133.4, AP001690.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC009274.9, AC005823.1, AP001331.1, AJ271736.1, AL136133.14, AL031671.12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC063947.30, AL161450.14, AL009172.1, AL138479.4, AC018469.5, AL359986.15,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AL133417.10, AC087083.2, Z97196.1, AP000457.3, AL360270.18, AL033392.5, AC023134.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL158201.19, AC079177.21, AC004820.2, AC024093.46, AL359380.16, AC006578.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| AP001669.1, AC087312.8, AC006365.3, L29074.1, AL359204.10, AC011912.7, AC073323.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AL121933.15, AC007748.2, AL359922.10, AP002848.2, AL133553.9, Z72001.1, AP002982.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AC078777.15, AC009037.6, AL359077.10, AP000687.2, AC007482.7, AF235098.1, AC004617.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL591046.4, AP003479.1, AC006249.1, AL355357.13, AC005951.1, AC004782.1, AL121841.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL009174.1, AP002532.1, AL135790.7, AL133467.4, AL359265.8, AC007037.4, AF042091.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AP001817.2, AP001672.1, AC026164.5, AL355478.16, AC020987.8, AC023469.6, AC021713.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC068660.3, AC083860.2, AC012446.2, AC010482.7, AL355888.3, AC011230.3, AL133480.9,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AC026203.3, AP000650.4, AC090710.16, AL590682.9, AL121788.17, AC004998.2, AC026202.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL137248.21, AC025439.4, AL163280.2, AL391623.13, AL354828.12, AL050309.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AC018951.8, AL109755.14, AC019050.4, AC008069.3, AC005859.1, AC002288.1, AC002074.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL136520.3, AC003984.2, AL096829.17, AC034242.5, AC010528.8, AL163952.5, AL159982.17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC005883.14, AL513342.7, AC002367.1, AC083865.2, AC008486.6, AC008716.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AL035411.27, AC006516.10, AL157902.6, Z92540.1, AL355375.17, AL390836.12, AL390857.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| ACMOSS 1, D8(459.1, ALOZ1957.1, ALOZ1957.1, ALOS1957.1, ALOS1957.1, ALOS1957.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| ACUIDO311, ALS91304-16, ALS9105041, ALS9105051, ALS910305, ALS910301, ALS910305, ALS9103 |
| ATT 25005013, ALCONOMO 14, ALCONOMO 14, ALLONALLI, ALLISTORILI, ALLISTORILIO, ALIANDER 12 ALCONOMO 4 ALCONOMO 4 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 3 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 ALCONOMO 5 |
| ALM 1203(13), AC020/OH.3, ALZ/1/135(1), AL COCCOSTOUTS, ALGOSTOUTS, ALGOSTOUTS,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| ALISSASTI, A. ALSHSRI, P. A. COURORGE, A. (ALORSHI, A. MAGORIA, A. LUSHSSI, I. A. LUSHSER, A. ALSWARGA, A. LUSHSER, A. ALSWARGA, A. LUSHSER, A. ALSWARGA, A. LUSHSER, A. ACOURDER, S. A. ALSWARGA, A. LUSHSER, A. ALSWARGA, A. COURDER, S. A. ALSWARGA, A. ALSWARGA, A. COURDER, S. A. ALGERS, A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, S. A. ALGERS, A. A. A. ALGERS, A. A. A. A. A. A. A. A. A. A. A. A. A. | EIEZECKON, AWGORINA, AWGORGA, BENENZES, BEINDYSR, AWGORIZO, AAAGOGTS, BEISTGAG, BEINGER, AMGORIZO, AAGOGTS, BEISTGAG, BEINGER, AAGOGTS, BEISTGAG, AAGOGTS, AAG | ALS300'1, ALS300'A, ALS304'A, LAS3566, ALQ3585, ALQ3131; BCG4289; BESSESSE, BELGGASSE, BESSESSE, BELGGASSE, BESSESSE, BELGGASSE, BESSESSE, BELGGASSE, BESSESSE, ARGUSTS, BESSESSES, ARGUSTS, BESSESSES, ARGUSTS, ARGUSTS, ARGUSTS, BESSESSES, ARGUSTS, ARGUSTS, ARGUSTS, BESSESSES, ARGUSTS, ARGUST, ARGUST, ARGUST, ARGUST, ARGUST, ARGUST, ARGUST, ARGUST, ARGUST, |
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| 15 - 1624                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 15 - 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| 1-1610                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1 - 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| 422672                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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| 19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| HAICP19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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| BE28895, N55929, AV698875, BF23880, AA34859, AV689303, T78749, BF736483, BF674953, W8249, W5467, D12186, AW961934, BF20837, AW418939, AW100980, A522016, R91823, AW193669, W81348, AV694579, W5619, BE803239, A/739123, AK0017041, AJ2781501, AC004979, A AC0063961, A AC006396, A AC006992, I | ALE 1964, ALS 1964, ALS 2568, ALS 2568, ALS 2565, ALS 25 | ATT-651, AU11990, AU118010, BC329904, ARMORG, ARMORTY, ARRITZAS BIGRI446, BEB1479, BESSESSA, AU12990, AU118010, BC329904, ARMORG, ARMORTY, ARRITZAS BROBSES, AU12990, AU109078, BESSESSA, BESSESSA, BESSESSA, ARRITZAS, AU12906, AU104694, WT2461, AU115730, BROBSES, AU104784, WT2461, AU115720, AU104605, AU104605, AU106050, AU1060 |
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| 12//                                                                                                                                                                                                                                                                                           | 15-1674                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 15-1503                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                                                                                                                                                                                                                                | 892971                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 656755                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                | 24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 25                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                | HAMGR28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HAPBS03                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| AW135722, AI476168, AI225142, AW468954, AW662675, R98339, BF701626, AA219273, AA894959,                                                                                               |
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| AW131851, AI935548, AW020315, AIZ/3292, N4Z/71, AA483620, AW020778, AU123385, BE/89622, AA806664, R76355, BF798339, AU143059, C01324, AA477442, AA278394, AA360766, AA493588,         |
| D57433, AA055730, AI263848, BF568115, AA355957, C16574, BE768067, BE257278, BE769335,                                                                                                 |
| AI871532, BG056236, AU157375, C15332, BE768128, C15888, AI572258, BE832706, AA127285,                                                                                                 |
| AA213389, BF568943, AA306589, BF768330, AI419087, AW352394, AI301771, AW948844, C16185,                                                                                               |
| AW352393, AI086134, BE768255, AA379170, AW150588, T05903, AI868436, AW607253, T34681,                                                                                                 |
| D56966, T05872, A1383207, T83511, AW386700, AA360855, A1553717, BE002352, AA749012,                                                                                                   |
| BE255441, BE407649, AA318547, BF916812, A4147990, AA9484636, AU126576, D58170, D81687,                                                                                                |
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| BEXOCO397, BE326349, C10337, AW 130637, LD4212, AW 501373, AK 034644, AK345010, BE170370, AI240376, BE973789, AA114282, AW 891081, AW 965974, AI 045469, AA 278975, AA 344020, N55736 |
| D57510, AA779191, R33042, AA531526, AW891054, BG034932, AA641391, AF000364.1,                                                                                                         |
| AL109936.10, BC001449.1, AL161799.19, Z82022.1, AL137459.1, AF219137.1, AB056809.1,                                                                                                   |
| AL359618.1, AL117432.1, AB062978.1, AB056421.1, AL512746.1, AB047904.1, AL050149.1,                                                                                                   |
| AL133640.1, AL117435.1, AF061943.1, AB055374.1, AB060916.1, AB060826.1, AL512750.1,                                                                                                   |
| AL137557.1, AK025967.1, AL137648.1, AK027213.1,                                                                                                                                       |
| BC004958.1, AL512689.1, AL133560.1,                                                                                                                                                   |
| AK025084.1, BC003548.1, AF090901.1, AL512765.1,                                                                                                                                       |
| AK026927.1, AF125949.1,                                                                                                                                                               |
| AL049430.1, AB056420.1, AK025312.1, AL512718.1, AL049314.1, AL353957.1, AL137550.1,                                                                                                   |
| AK026542.1, AK0245241, BC003858.1, AK026741.1, AK027146.1, AF056191.1, BC008365.1,                                                                                                    |
| AL050277.1, AK026504.1, AK026045.1, AF225424.1, AL137271.1, AK027164.1, BC006195.1,                                                                                                   |
| AL162002.1, AK026086.1, AL512684.1, AL080159.1, BC008899.1, AK026959.1, AL096744.1,                                                                                                   |
| BC003122.1, BC006494.1, AK000718.1, BC001967.1, AF091084.1, BC008387.1, BC004951.1,                                                                                                   |
| AL133016.1, AK025254.1, AL137527.1, S78214.1, AK000486.1, AL389939.1, AL050024.1,                                                                                                     |
| AK026480.1, AL122050.1, AF132676.1, AF061836.1, AL137538.1, AK025015.1, AK000323.1,                                                                                                   |
| BC004556.1, AL133565.1, AL122121.1, AB049892.1, Y16645.1, AF177336.1, AB060852.1,                                                                                                     |
| AF090903.1, AB052200.1, AF271350.1, AK000083.1, AK025092.1, AL359601.1, AF260566.1,                                                                                                   |
| AL389982.1, BC006807.1, AK026532.1, AL137463.1, AK026865.1, AK026408.1, AF026816.2,                                                                                                   |
| X72889.1, AL137526.1, AL049347.1, AK027096.1, AK026522.1, AL359583.1, AF110640.1,                                                                                                     |
| Y14314.1, BC008417.1, AF217982.1, AL122093.1, AL389935.1, BC007021.1, AK024538.1,                                                                                                     |
| AK026534.1, AK024588.1, AF106862.1, AB052191.1, AK026583.1, AJ242859.1, BC008717.1,                                                                                                   |
| AK025772.1, S77771.1, AL42082.1, X65873.1, AK026593.1, AB055361.1, AL080060.1,                                                                                                        |
| AB051158.1, X82434.1, AF097996.1, AK026597.1, AK025414.1, AF183393.1, AL133557.1,                                                                                                     |
| AF252872.1, AL133113.1, BC002733.1, AK026462.1, AL080124.1, BC008488.1, BC008070.1,                                                                                                   |
| AL133080.1, AB055370.1, AK025339.1, AB055315.1, AL512733.1, AL162006.1, AL049452.1,                                                                                                   |

| ### (### 17800144), Z79721, AB075861, AR007610, AF152981, AF11112.1 AR0071161, DROMHRI, APGPR441, AL121101, AL559941, AF127191, AB048951, AB0761161, AL1375601, BC005168-1, AR0267441, AL1368441, AR0257091, AR027091, AL1174601, AM052981, MEGMS441, AR027091, AR027051, AR107091, AR027081, | DERODSHAP, AWSTRON, MASTRON, DAWSHOR, AWSTRON, AWSTRON, AWSTRON, BEESTHI, A<br>MISTOSI, AMISSEZ, AMISWIGA, AWSTRON, AMISSEZ, AMESSEZ, AMESSEZ, AMESSEZ, AMESSEZ, AMESSEZ, AMISWIGA, AMISSER, AMISWIGA, AMISSER, AMISWIGA, AWSTRON, AMISSER, BENGHOW, BECARRENTEZ, AMISSEZ, AMISTROSEZ, AMISSER, BENGHOW, BECOMESSER, ALLIANDES, AMISSER, A | AGS0731, ALS0732, BEZ1020, BEZ1205, SHE BEZ120, SHE BES103, REBGGTI, BELL HG45, ARROWNI, AVAIGNOM, AND SHE BEZ120, SHE BEZ120, SHE BEZ120, SHE BEZ120, SHE BEZ120, SHE BEZ120, SHE BEZ120, SHE SHE SHE SHE SHE SHE SHE SHE SHE SHE | ALS 92596, AL22544, RE191416, AL53189, AL521416, AL525358, AL556444, AL52631, AL53389, AL53644, AL53631, AL53389, AL53644, AL53631, AL53389, AL53646, AL53654, AL53646, AL5364 |
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| ALMSTON DETECTION   ALMSTON   ALMS |
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| AC018811.4, AC0076852, AL121601.13, AC0048051, AL353377.18, AL359397.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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| WY2075, H0021, R2026, H000H, H0171, H1140, H11808, W0029, H18010, H1787, AASSR10,<br>AAL8604, T367, H07305, R9971, H1361, AA32609, AA006672, BF45667, H01155, W4428,<br>AAL8604, T3626, H9020, AA31917, H9107, AN00542, R5676, K13887, H01155, W4428,<br>AASSW, M35148, AA416643, AC014627, AF1518081, AF096601, BC001192, I-72716,<br>H0025, F1077, R2666, F7094, H0350, H0780, H0780, H27368, R87112, H60187, H60393,<br>H07412, H4495, R71661, W31381, AA16892, AA188345, AA41906 | W27833, AIROTO4, AAROOG IJ, BF432929, AA768248, A1370876, AV748724, A1291737, 196013,<br>NOKO1697, A1633038, A1784315, BE546233, BF980899, BF977483, AL1384794, AL1328554,<br>AL121755, 22, | MW94217, IBRN799, BRG0218; BEN2972, BEL3929, BEL3018; BER3015; BER7845; BER7845; BER7845; BER78459; BER78519; BER7859; BER78519; BER7859; BER7859; BER7859; BER7859; BER7865; BER9781; BER9781; BER9781; AL52549; AAA3879; BER9781; AAV3966; AAV3966; AAV3966; AAV3966; AAV3966; BER9164; AAV3966; AAV3966; AAV3966; AAV3966; BER73767; BER9781; AAV3966; BER79767; BER97916; BER9791; BER9781; AAV3966; BER79767; BER7916; BER9791; BER9786; BER7966; BER7787; BER7787; BER7916; BER9791; BER97819; BER9789; BER9796; BER7787; BER7782; BER7986; BER7787; BER7782; BER7986; BER7787; BER7782; BER77782; BER77778; BER77782; BER777786; AV777782; AV777782; AV777782; AV777782; AV777782; AV777447; AV777443; AV777                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | AWD27905, AUGS-MA, ALDPY3-AVT2999, LINSSA, MAGOS-LEBUS-2488, ACCORDOFF, ACCOUNTED, ACCOU |
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| ALIS6970.21, 297876.1, AC008946.3, AL020236.1, AC00738.3, AL451075.15, AL390374.16, AC0264.13, AC0019497, AC0091208, AC0002666, AL502715, AL290724.1, AL159784, AL1514546, AC008091.3, AC0007526, AC00246.1, AC00649.19, AC002301.1, AC004160.1, AC004082.3, AC008726.1, AC00649.19, AL1209224, AC015501.8, AL058201.5, AC00871.7, AC00490.2, AC00649.19, AL1209242, AC015501.8, AL058201.5, AC00891.2, AC00649.19, AC1097434, AL1215781, AC008934, AC00892.3, AL03871.7, AC006490.2, AC008766.4, AC006922, AC006980.3, AC008934, AC007897.3, AC00946.6, AC006492.2, AC009981.3, AL3315.13.4, AC006491.1, AC00940.3, AC00946.3, AC00946.3, AC00946.3, AC00946.3, AC00946.3, AC00946.3, AC00946.3, AC00946.3, AC00946.3, AC00940.3, AC00940. | AI827239, AW104045, AL536345, AL096774, 9, | BEGGTO, ADSTACLA ANY STRENGEN, AND STRENGEN, AND STORAL AND STRENGEN, AND STORAL ANY STRENGEN, ANY STRENGEN, AND STRENGEN, ANY STRENGEN, ANY STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND STRENGEN, AND S | AWWG2384, AWWG522, AAGISIR, AVR064544, AVR06444, AVR06418, ARIAFIA, AVY20132, AVX2014, AVX201 | AA713518. AA807610. AW104604. AA830415. AW975518. AL138824. 19. |
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| HISTORY, ALSEAG, ALSINSKY, LANSINGA, BERTZYZ, AAROBY, ARGOSZ, BERGYJZY, ARGOSZ, ARGOSZ, ALSINGA, ALSINGA, BERGYZY, ARGOSZ, ARG | RIPGAD54, BE3302, IRPAG58, BE127389, BE32490, BE608522, BE93914, E1390135, BE5009, MW996894, BE327786, BE73014, BE34000, BE1277864, BE740138, BE34000, BE227786, BE740148, BE34000, BE227786, BE37614, BE3761, BE3761, BE3761, BE37614, BE3761, BE3761, BE3761, BE37614, BE37614, BE37614, BE37614, BE3761, BE37614, | AL525531, BG034956, BE858832, BE897817, BF510434, BG253874, AI656560, AI628821, BF215392, |
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| 15 - 1276                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 15 - 2084                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 15 - 1765                                                                                 |
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| HCE2F54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | н<br>СВЗСФ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | HCE5F43                                                                                   |

| PER24494, AUGOTY, R.052396, WAY59490, AUGUIZ, BF342815, BF97788, AUTSST7, AAPTOI 34, BF124494, AUGOTY, R.0525, AUTSST7, AUGUST7, | PEG-2012 J PES-2912, JB-94483, IB-966606, BES-444530, BES-44215, BES-15319, A. A199526, BES-87064, AW016800, AD937454, A.7109034, AA416007, AW046450, N75646, BES-41415, AW960857, BEG222204, A.7A07456, BES-54560, AM116034, AAA107342, AR8413, TZ3840, AA446794, AAA222874, MR6414, A.7407476, BESS-5456, AW116034, TAS-894, AW19717770, BESS-96, BESS-96, AWS-144, AWS-96, TES-804, AW19717779, BESS-96, BESS-97577, AW197166, BEG-75295, RED-56, RED-56, AWS-946-74, AWS-94074, AWS-94074, AWS-94074, BESS-97, AWS-94074, AWS-940 | HOGT WOLLS, HESWORD, AVTEZDES, HESTORGY, BAPESCURY, AVESTURS, AVESURGE, AVERSERS, ANAWERSER, AVERSER, |
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| HGEWEZO 444 | 543370 | 1 - 871 | - 888 - 12 |                                                                                                                                                                                                                                                                                                                                                                                          |
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| ACOUNTIA, ACOURSMIA, ACOURTIA, ALGAPSA ALGALIA, ALDSSHIA, ALCASHIA, ACOURTIA,  AD13465, AND09453, AA47742, AA152289, BE219294, T27069, AIJ45607, ANW52105, AI807602, AA224651, AA027444, BE21940, AA065234, NJ0888, AA22545, AA0019102, BF97165, AA2151849, AA224651, AA02744, BE219404, AA065234, NJ0888, AA21545, AA019103, AA177615, AA2151849, BR8841, BA121961 (68, N9522, BF762367, AV06775, T41162, BE66404, R5457), BED07275, BR8856, AA113946, AA113961, BA14394, AA113964, AA113961, BA14394, AA113964, AA113961, AA113961, AA113964, AA113968, AA117986, AA177986, AA117986, AA11798 |
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| NAT745917, AVT45600, AVT717084, ANT71064, AVT71064, AVT7 | AMGELTI, BFZ228A7, AAGSGS, HA9029A, WH2942, AWD7019A, AASGIST, (1692)A, A999187, AMWSS297, AA16972, BES4867, AGS1945, AA70799, AA535510, BGG59719, AG80791, AZ10977, BHZ406, AA524577, AAMG2981, AA26529, HI6756, AB90700, AW970783, BESS8688, AG906027, AB907685, AV709230, BEZ20337, AW194554, AA365390, AA678861, BE707377, AL122003.17, AB907895, A | AW964468, AW975618, AV1211, AW966633, AV738928, AW994645, AV727978, AW966633, AV72220, AV701357, AV721079, AW966533, AV72220, AV701357, AV721070, AW975310, AV721070, AW975310, AV721070, AV72100, AV723104, AV72100, AV723104, AV72104, AW96405, AV72104, AW72305, AV72104, AW972305, AV72104, AW996042, AV74060, AV7730164, AV72301, AW996042, AV721046, AV771040, AV772011, AW996042, AV711046, AV72011, AW996042, AV711046, AV72011, AW172031, AW996043, AV72011, AW172031, AW996046, AW97334, AW996013, AW996014, AW172031, AW172031, AW996066, AW97334, AW996014, AW997804, AW997804, AW997804, AW997804, AW997804, AW997804, AW997804, AW997804, AW997904, AW997804, AW99 |
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| WATT1982, AW96664, AY72010, AW36209, AW96156, AW96166, AV171983, AW973007, AW71982, AW96664, AY72010, AW36662, AW71916, AW71978, AW72010, AW71984, AW71978, AW71978, AW72010, AW71984, AW71978, AW71978, AW72010, AW71984, AW71978, AW71978, AW72010, AW71984, AW719784, AW95618, AW97348, AW72016, AW966197, AW720164, AW720164, AW720164, AW720164, AW720164, AW720164, AW720164, AW720164, AW966197, AW720164, AW966197, AW720164, AW720164, AW966197, AW720164, AW9720164, AW720164, AW9720164, AW720164, AW9720164, AW9720164, AW9720164, AW9720164, AW720164, AW9720164, AW720164, AW9720164, AW720164, AW720164, AW9720164, AW720164, AW9720164, AW720164, AW9720164, AW720164, AW9720164, AW720164, AW9720164, AW9720164, AW720164, AW9720164, AW9720164, AW9720164, AW9720164, AW9960124, AW996014, AW9960124, AW99 | BF691R28, BE463583, C06338, AA826324, AA622862, AI890787, AA775044, BE566444, AA621523, BF207929, BF208992, BE928360, BE568426, AW873470, BF036636, AI632964. |                        | EIPENTIOI, BESGODO, ANDZSI, IEROPOS, AAGAST, BGISOLZ, ARGISOOI, ANTZES, AAO920T, AVIZOSSO, ANGWISO, ANDZOS, ANGRISO, ANDZOS, ANGRISO, ANDZOS, ANGRISO, ANDZOS, ANGRISO, ANDZOS, ANGRISO,  MIN'SCHES, AJBRIGA, TAWBRISS, ANYSRON, SADOPTIA, ANALOGA, ANYEGAS, ANYGAS, ANGRAS, ANG |
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| AVID1862, VAW66644, VALDOIB, AVIGEGG, AVID1863, AVID1983, AVID1984, AVID19843, 4443, AVID1984344443, AVID198434444444444444444444444444444444444 | BF691828, BE463583, C06338, AA826324, AA622862, AI890787, AA775044, BE BF207929, BF208992, BE928360, BE568426, AW873470, BF036636, AI632964,                  | AA722669, AC005035. 1. | BEPSH 101, BESTORO, MANDEST, IL BERONGA, AND ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKEST, BEST ACKE | AWSG448, AUSBOIT A WARRSSS A ATTSORS, ALMOTSTA, AUSHGSA, AWARDSSS, AUSPOSTA, AWARSSS, ATTSORS, AWARSSS, ATTSORS, AWARSSS, ATTSORS, AWARSSCI, BEG10593, AWOGSTG, AWOSTGO, BELBSSQ, AWOGSZT, AWOZTGI, BEG10593, AWOGSZG, AWARSSCI, BELBSSQ, AVYGGDG, AVAGGDG, AVAGGG, AVA |
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|            |        |          |           | AC018696.4, AC007263.4, AP0017471, AC0076794, AC006458.2, AL133448.4, AC009412.6, AC0064911, AC073897.6, AC007053.3, AC0046551, AP0002151, AC004998.2, AC002350.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| +          | 20000  |          | 0071      | AC012309, 7.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HCWUM50 54 | 639037 | 1 - 1414 | 15 - 1428 | AW967979, AA937109, AA465498, AA465250, AW967765, AA262829, AA743297, H93605,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| 15-1691 | HDABR72 55 1301517 1- | AA32-051, AW4-0216, IP3-064, AW2-062-8, AUI ISR07, BES1214, AW9-68591, BE93-4985, AA4651-42, AA3-09767, BE93-964, AA2-0469, BE702-09, BE702-09, BE102-06, BE702-09, BES18589, BE162-646, ALI 18-047, ALI 58-07.15, AP5-053-01, AK000-0951, AK001-156, AK00-0616-1, AK00-0 | 1301517 1-1677 15-1691 |
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|                |        |          |         | AC0922571, AT0011/21, AC054242,3, AC016850,3, AC01485.6, U6/8011, AF2139571, AC0922571, U025311, AL161756, AC07671, AL04958.811, AF167791, AL056841.6, AC07671, AC076 |
|                |        |          |         | AL359513.12, AC011480.3, U18398.1, AL121581.41, AC008101.15, AC018644.6, AP0119/2.4, AC020740.5, AC005911.6, AL163282.2, AC005484.2, U18396.1, AC007957.36, AF015148.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                |        |          |         | AL139113.21, AC034145.5, AC069255.18, AC005234.1, AL023803.3, XS5923.1, AF109907.1, AL040835.3, AC007324.5, AB0708K3.1, AC00501.1, AC004008.1, AC007334.8.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                |        |          |         | AC00807923, AL512666, U826713, AC0050473, AL034420.16, AL050328.24, AC004813.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                |        |          |         | AL451103.7, AC073651.23, AF042090.1, U02532.1, AC073581.23, AL031005.1, U18390.1,   AL0087251                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                |        |          |         | AP000161.1, AC035150.1, Z82901.1, X55922.1, AC008622.5, AL354915.5, AL445189.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                |        |          |         | X76070.1, AL035696.14, AL122035.6, AC018633.2, AL359751.12, AC034186.4, AL137229.4, AC004031.2, AL03181, AL131030.17, AC004470.2, AL150185.8, AL04060.118, AC004363.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                |        |          |         | AC006329.5, AC074191.3, AL158218.11, U18400.1, AL132987.4, AC090841.1, AL357515.26,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                |        |          |         | AL356020.3, AC009506.5, AC005785.1, AL590709.5, AC002365.1, AL049647.7, AC004662.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                |        |          |         | AL122013.5, AC005664.2, AC073347.3, AP001731.1, AC008119.6, U67221.1, AL158141.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                |        |          |         | AE021134.1, AF001888.1, Z99129.1, AE357518.13, AE359037.14, AE132642.4, AC012306.11, X55927.1. AE133332.12, AC004257.1. AC005215.1, Z83840.7, AE590076.3, AC005632.2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                |        |          |         | AC005918.12, AL035450.1, AC006270.1, AP000556.2, X55932.1, AL158159.14, AL109825.23,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                |        |          |         | AC009996.7, AL031661.28, AL512430.14, AK024206.1, AL118501.22, AP001434.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                |        |          |         | AC073145.8, AL139327.18, AP000348.1, AC008744.6, Z95114.19, AE006463.1, AL359085.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                |        |          |         | AC02/319.5, Z/4/39.1, AL356801.5, X341//.1, AC0/2032.6, AC004838.2, AF1969/1.1,<br>  AT302110.12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                |        |          |         | AF085913.1. AL132874.30. AL445212.9. AL080242.11. AL035446.4. AL121989.12. L47228.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                |        |          |         | AL031681.16, AL1616664, AC017079.5, AC006433.18, AC009131.6, AC008555.5, AF015150.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                |        |          |         | AC010422.7, AC004028.1, AL050341.18, AC087239.18, AC006327.3, AC005341.12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 23 00 4 00 011 | 102703 | 1 2423   | 16 2447 | AC019205.4, AC005755.1, AC009470.4, AF015153.1, AC011484.4, AL022324. 1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                | 7007   | 1-040    | Ė       | EE/67008, AW976840, AI640606, BE178142, BE177971, AW502888, AA977785, AI979247,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                |        |          |         | AW503911, AA971157, AL135446, T27536, AA491080, W74279, R07065, AI687230, T27535,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                |        |          |         | AW816221, AA436906, BE151455, BF510035, BF803181, BE151443, AA152394, AW505067,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                |        |          |         | BG003144, AA761110, AA377229, AV648450, BE671931, AI873792, AA397568, AA399529,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                |        |          |         | AA6/9080, A1382296, AV648107, AV648212, AV648357, A1915254, A1741550, K50250, A1920850, A1018184 A A 202114 A124858, R81654 A1126673 A A 152500 RG057181 A A 148355 RF817269                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                |        |          |         | AF222340.1, AF183569.1, AF106037.1, AB011097.1, AC008906.5, AC009073, 8,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| HDPC101 58     | 740748 | 1 - 6093 | 15-6107 | ATTITIONS AWOSO367 DE702861 DE672087 DE720420 DE717152 DE7770039 DE718805                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| AW971539, AL079949, BE770941, BF687684, BF132755, BF727151, BG009815, Al703121, Al066742,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| BE908461, BE717019, AW444843, W61007, AD499993, AW502524, ALID0343, AR599083, AA5953478, AW467411, BF515251, BF063545, BE717046, BF042969, BE673935, AU154204, AA292253                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AA838717, AU145486, AI273190, AWS12776, BF727150, AI084372, AI597583, AI457829, H99255,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AW474793, BE327577, AI697937, AI167388, AI684736, W69563, W31042, AW753588, N98496,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| A1307397, AW61887, AW241267, BF198110, W60918, AA291214, AW316965, BF109819,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| AA988541, AA908177, AA014524, AA651802, AA304541, B5556255, AA045612, BF431421, A261626, BF214133, AA972952, A1334810, R80993, A1539739, D62886, A1611313, N28297, H99484.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| A1825223, AW938439, T65655, A1221607, AA169878, AA435697, AA262010, W69419, F11961,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| T34633, A1873428, A1457907, BF103809, T65584, A1695552, AA126467, AA641749, AW882312,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| NS2582, BG149944, BF669976, D57676, AA169566, AA126647, F09610, AA446424, R78978,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AA291524, D6273, T15751, AA65880, AA62880, A196715, C18887, AA649257, A1431924,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| AAZZOOLO, 12001, 12011, 12012, 1617, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, 1620, |
| A1312790, A1260552, AW65463, BC222875, A1039809, A1223626, BF725884, A1281584, A1281284, A128184, A128184, A1281284, A128184, A128184, A128184, A128184, A12 |
| AI251203, AW268329, AI254770, AA602906, AW673941, AV764259, AV647070, AI569086,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AW303098, AAS24800, AI249886, AI251241, AW474921, AV737641, BE042006, AI082510,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AW971342, AW088049, AW068007, AK001067.1, AL161732.7, AC007688.15, AP001718.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| AL163281.2, AC009134.6, AC068724.7, AL117336.22, AL359382.23, AL121890.34,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AC007540.3, AC008651.7, AL139405.11, AL031388.1, AC069255.18, AC006013.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC015977.9, AC010742.4, AC008891.7, AC025280.4, AC018764.6, AC005747.1, AL158052.10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC011247.10, AC002072.1, AC007792.1, Z82203.1, AC004593.1, AC010616.5, AC068799.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL121656.2, AF020503.1, Z83822.1, AC005874.3, AF134471.1, AC073542.4, AC004752.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL161757.4, AL023575.1, AC006021.2, AC004638.1, AL161670.4, AL117377.18, AL050335.32,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL590636.12, AC002287.1, AL139187.19, AC0687226, AL137061.12, AL163052.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL051132.2, AP00126.1, AL137885.21, AC00725.2, AC004953.1, AL137933.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| AC005538.2, Z82244.1, Z83845.14, AC016831.1, AC009505.3, AC004949.1, AC004965.2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| AC005358.1, AC007388.3, AC007462.2, AC073581.23, AC008513.7, AC006483.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AL356244.12, AC002368.1, AC026162.5, AC020741.4, AL096814.26, AL390755.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC005514.1, AC008474.7, AC007151.2, AC011359.5, AP002852.3, AC008066.4, AC004032.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL034405.16, AL442064.10, AC019046.4, AC006115.1, AP002851.2, AL138725.19,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| ACUZ2306.11, ALI31 100.10, ACU3202.27, ALU32012.11, ALI31 100.10.11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| MURDIOGAL, ALOSSOB, I. M. PETZEA, AFRIDAZI, M. MEDIOZI, MAIGSA92, ACOUGHOST, ACOUGHOST, MAISSOB, I. M. PETZEA, G. M. | ALGHONO), ALGHONG, BERSILIS, BERSILION, BENGOSSA, BGILSKOF, BERSPSYO, BESSZSA, ALGHONO), ALGHONO, BERSPLOS, BESSZSA, ALGHONO, BERSPLOS, BERSPLOS, BESSZSA, SANGHONG, BERSPLOS, BERSPLOS, BESSZSA, ALGHONG, BERSPLOS, BERSPLOS, BESSZSA, ALGHONG, BERSPLOS, BESSZGA, BESSZGA, BERSPLOS, BESSZGA, BESSZGA, BERSPLOS, BESSZGA, BERSPLOS, BESSZGA, BERSPLOS, B |
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| <ul> <li>HISHOGAR, T211, PB3230, HISHOGAS, PB34042, PTG4138, BTG405, BEB237, PB181044, PB34042, PB18216, ALSPRIJS, MAGD705, BB8237, PB2457, BRSHIGM, PB94043, AI40705, BIG107249, AI86465, AIR2674, AI657756, AL513907, AMVISTIS, AUSTOTI, BESPOGA, AISOTOG, ALSPEGA, AISOTOG, AIGHS AISOTOG, AIGHS AISOTOG, AIGHS AISOTOG, AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGHS AIGH</li></ul> | AI193249, AI809829. | ARI, 25411, IRCZ15 (Q.B. PER1637; ALIJ312), REVSSSIR, BER05200, WY72229, BEF1643; ANY 170909, AIMOST31, BEF30298; AA972732, AAG75 184, AWI 177905, BEL41799, ANWEGST30, BEG66730, ANY 151928, BEF41798, ALIJ57405, AND 1804, AWY 17595, BEL41799, ANWEGST30, BEG66730, ANY 175904, BESSSSS, ALISTSS, AAD 1805, AA70 16706, ANY 175904, BESSSSS, ALISTSS, AAV 17506, AA70 16706, AA70 17507, AA105572, AA105740, AA70 17507, AA70 17506, AA70 17507, AA70 17507, AA70 17506, AA70 17507, AA | AC005946.1, AC018755. 3. | A. A. A. A. A. A. A. A. A. A. A. A. A. A | BG058578, D20888, AL034424, 9. | BEWGSPO, BE'D155, A.J.5158I, BERDOZA, ALBOQAL, IRRZDRAJ, BEPGRSSS, ATIGGGG, BERSTSOT, ANYSPOR, ATMERICA, BERGGL, BEIGCZ4, AVTJ1629, AVG9640, AVTSC11, AVGSC11, AVG |
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767            | 15 - 2687                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 15 - 728                 | 15 - 1635                                | 15 - 1727                      | 15 - 1655                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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753             | 1 - 2673                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 - 714                  | 1-1621                                   | 1-1713                         | 1-1641                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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                                                                                                                          | HDPHI51                  | HDPJM30                                  | HDPND46                        | HDPOJ08                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| ALISSON, AMSROZ, AANKRSK, BEPPOROE, BEIGRAK, BEIGROZ, AASSHTJ, AMSKSS, AASSHTJ, AMSRSS, AASSHTJ, AMSRSJ, BEPTOR, BERNGK, AMSRSJ, AMSRSSJ, AMSRS, AMSRSJ, AMSRS | BELSONO, BED3408, RV95346, WAP9660, BES5070, BR98238, ARB2171, BES41597, AND BELSONO, BED3408, BES7138, WAP9610, AND SOSTO, BR98238, ARB2171, BES41597, AND BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, BES14597, |
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| M. (2009) M. (2009) M. (2009) M. (2009) M. (2001) M. (2009) M. (20 | ACID 5990, ALADICA, ANNONGA, ALASHGO, AWASHA NA WALSASA, ALSHGA-H, ELEZZESY, BRTASEZ, 
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| . S. 1663                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 13 - 1063                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| AL515041, A1815383, AL513597, BE905408, AL513553, AL513907, AL514919, AL514803,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| AW0/1349, Al2000/1/, AL/02400, AL041/03, AW999049, BG1/9993, AL036390, BG10/044, AL04500, AL045500, AI33157, BG252929, BE877769, BE048179, AL119791, BE965556, AV755290,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| BF054789, AI687728, BF673434, AV682809, BF344652, AV704928, AI538716, AL513741, AV681872,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AV682289, AV682266, BF981774, AV727776, BE966388, AV682249, AW089572, AI873731,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BE048081, AL036759, BG033403, BG151247, AL514627, AV710608, BG178809, AV655645,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AV682672, BF793644, A1440426, ALI 20736, AW117882, ALI 21365, A1969567, A1281779, BG259801,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| AV 755619, AW627211, AL515175, AL549250, AL036002, BE018711, AV 762468, BG106524, REGREGAGA RG26604, AL756067 AR80503                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| A1349937, BG029399, BG180996, A1686926, AL513693, BE887488, BF817392, AL513803, AW103371,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| BF036115, AV758668, AV732941, AV711509, BF342709, BF726297, AW195957, AV681647,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BE968041, BG108147, BF726001, BE967113, AI521012, AW238730, AI349004, AV757797, AL513837,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AV682466, AI366549, AV726951, BE777769, AV723953, BG112879, AV681759, AW074993,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AA640779, AI343112, AL036980, AA613907, BG109270, AI340582, BE781369, BG179633, BE048135,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| BE048163, BF037097, BG121222, AV758822, BG027204, AV758592, AV682479, BE968552,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AV757455, BE880190, AI690835, BE963035, AI920968, AI818683, AI499393, BE047859, AV682267,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL120854, AV682082, AV758179, AV757012, AI934036, AL513753, AI282655, AI439087, AV758217,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AV756477, AV682441, BE048026, AV681951, AV763915, AI678302, AI609592, BE048319,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AV764059, AV706777, AV710479, AW301409, BF726421, AL529946, AI699857, AV682772,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| A1469532, A1207510, BE969709, AW467961, AV682792, AV717179, AV758806, A1969601,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AV709517, AJ349614, AL514791, AJ866608, AV755311, BF340031, AV682330, AJ580190, AV681857,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AV711924, BE881155, AW166645, AI349598, AI906328, BG109125, BG114104, AV681668,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BE613622, AV708119, AW274192, AV682333, BE964486, BG031815, AW080838, AV755613,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AV660662, BE909549, AI597918, AF311287.1, AK024001.1, BC008877.1, BC008417.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| AL136586.1, AF078844.1, AL050393.1, AL389978.1, AF090934.1, AF125949.1, AL157431.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC008387.1, AL050146.1, AL442082.1, BC007021.1, AL390167.1, AL442072.1, AL133640.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL080060.1, AB056420.1, AL133016.1, BC008365.1, AB055303.1, AF090901.1, AJ242859.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| S78214.1, AF090943.1, AL117460.1, AL136787.1, AL512733.1, AF090900.1, AF090903.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AK026608.1, AF104032.1, AB048953.1, AF218014.1, AB049758.1, AL137527.1, AL110196.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL117457.1, AL133606.1, AL049452.1, AL049938.1, AK000212.1, AL110221.1, BC008488.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC003687.1, AL359596.1, AL359601.1, AK026865.1, AF111847.1, BC003683.1, AB060916.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AB048964.1, AB063046.1, AB047615.1, AB056809.1, AL136892.1, AL136789.1, AL050149.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| AL050108.1, AL136749.1, AB047801.1, AL122050.1, AK025339.1, AL162083.1, U42766.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AB050510.1, AB060887.1, AB019565.1, AK026045.1, AF106862.1, AL080124.1, AL133075.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| AL042314.1, AL060137.1, AL137263.1, AN023330.1, AL122033.1, BC001907.1, AL020744.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| A1366985, A1802826, A1270039, A1824557, A1628325, A1582240, A1583578, A1308035, AW268060,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| A1627909, AA493923, AL039287, AW302973, A1282967, AL042981, A1622926, A1559863, A1580290, A1571699, A1038154, A1677797, AW302073, BG105342, BF816041, AW084097, BF967265, A1824503                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| BF913615, AA731026, AW083804, AA878532, A1678446, A1318254, A1951222, AW193841,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BF816031, Al365256, Al446405, BE393551, BF817746, Al699154, Al285439, Al744243, F34309,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AA555145, BE974031, AA580663, AW081343, AI819516, BE613727, AI799313, BF868927, AI309306,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AW104141, BG107564, A1272116, A1433611, A1623388, AW025279, BF925370, BE294431, A1357191, A1437191, A14371 |
| AIR01561 AIGASCO AITRASCO PERANCAS AIRSCACA AVAILAGES, MADOLLS, TAWOOLOGO, MADOLLOGO AVAILAGES, MADOLLOGO AIRON AIRCHANNA AIRSCACA AVAILAGO AIRON SCACA AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHAN AIRCHA |
| AA835966, AI499986, AI689463, BF751997, AI499960, AI636507, AI803749, AI886055, AI873638,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AI378131, BF814357, BE875959, BG033220, A1682121, BE964645, BF726001, A1289791, BF924884,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AW089844, AI819016, AW029216, AW970048, AI568138, AI345471, AI613422, AW080335,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AI318609, AB020598.1, AC004126.1, AK023577.1, AK000546.1, AK000450.1, BC008673.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| U75370.1, AL13353.1, AL110171.1, AB048995.1, AF188698.1, BC003111.1, 105032.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| ALI32861, BC006091, BC006091, BC006091, BC006091, ALI321111,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| BC0001851, AL031346,8, AK0272441, S777711, AL137651, AK0007181, BC000386,1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| BC002524.1, AL035407.15, AK027113.1, AK000137.1, U39656.1, BC005816.1, BC001293.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| BC004336.1, AL136792.1, AF239683.1, AB063074.1, BC004874.1, AL133565.1, BC004943.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC002978.1, AF038847.1, AL359583.1, BC003548.1, AL136586.1, AL512719.1, S76508.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| BC005002.1, BC005858.1, AL359600.1, AK026571.1, AL137536.1, AL137711.1, AF274348.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AF274347.1, AL133014.1, Z49258.1, AL136984.20, BC004960.1, AK026408.1, BC001774.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AL136850.1, BC008649.1, AF245044.1, BC008895.1, AL162003.1, AF162270.1, AL117626.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC007571.1, BC007517.1, BC003682.1, AL137574.1, AK026627.1, AK025015.1, BC005843.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| U006861, AF040751, AL136752.1, AL137641.1, X99226.1, AL161427.16, AL161628.9,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| AF0009341, AF218005.1, X60819.1, AR024974.1, BC003569.1, AR026182.1, BC004431.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| AF000886.1, AK024747.1, BC007198.1, BC0082597.1, BC005402.1, BC005033.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| BC007417.1, AL136615.1, BC001328.1, AL133645.1, AL049382.1, BC006408.1, BC007355.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AB047801.1, AK027105.1, AF205861.1, BC007534.1, AL137660.1, AF155827.1, BC006807.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AC02447.4, AL0800601, BC004117.1, BC000550.1, AB050411.1, AR027104.1, AF090165.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AB0450341, AB0480141, L3011/1, AL0494601, AR0260341, BC0001331, AR0253411,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| ACO046664, IA.1376412, ACO100814, ACO06944, BRODGES,1, ALI376413, BRODGOOTJ, ALI356991, ARIHIIL21, BRODGAOTJ, ALI359911, DRS3981, BRODGEST, ARIHIIZA, BRODGEST, ARIHIIZA, ARIHIIZA, ALI369701, ARIHIILZA, ALI369701, AKO06651, AKO25407, ALI356971, ARIHIIZA, ALI696881, ALI696878, BRODGEST, ALI356232, AROUGEST, ARIGOGOST, ARIHIIZA,  AUWROJI SA, AWROJI SY, AWRZI STS, BEROS JO, BFO94022, BF3375SS, BF572692, AWR45544, AWI 76604, BF734294, BF928740, BF36061 S, BE169703, AJ230819, BF734231, AL133649.1, AZZ77791.1, AJ277790.1. | BF689672, BE387282, BB598209, BE386984, AA593894, BE893192, W22615, AA13475, BG006306, ATIF09121, BG006608, AA367857, AA341701, BG018403, BE368795, AA367892, AAV065363, BG006302, BF932070, AW948496, AK07737511, BC004282.1, AK027831.1, AK077891.1, | AMORIZON, BF966GA, AWISTRAW, HOUSTAG, BRSON, AATSEN, AWISTITOS, BEB27923, AMORIZON, AFTONO, AND AFTONO, AND AFTONO, AND AFTONO, AND AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AFTONO, AF | ALASTISTA, ALESGOR, ALSONO, TACS199, ALGSTS19, ALSTS109, ALSTS00, ERGODO'41, REPROBED'S REPROBED'S ALGSTSON ALGSTSON ALGSTSON REPROBED'S REPROBED'S ALGSTSON REPROBED'S REPROBED'S ALGSTSON REPROBED'S REPROBED'S ALGSTSON REPROBED'S ALGSTSON REPROBED'S ALGSTSON REPROBED'S ALGSTSON REPROBED'S ALGSTSON REPROBED'S ALGSTSON REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S REPROBED'S |
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| AC008064.2, AL357507.9, AP001670.1, AL137061. 12. | AA329666, AA664883, AL133353. 6. | WY72560, BEIGLÉS, MY13067, BET-BUSDY, ALTSROB BEFSTS, A1096457, BE941499, WSSB3, A1161240, N92226, AW69649, ALS6723, A093508, A087144, AA044208, AW113061, AL423547, A1221152, AN09714, H47284, A152542, AR09116, A1002491, TS270, AA04416, R84370, R2430, AA68606, AR027040, AR10388, BE1416106, EA44698, KR674, TS273, AA05915, S225099, AAV273857, AR08513, ASSA9717, AA051513, AA051513, AAV115145, AA08717, AA15904, AA025404, AW02614, TS374, AW05170, AW125164, AW02704,  AM 15/1714, AM25724, Be101914, AM51622A, AM5161 R BG16880, AW29391, BR135422, AM217144, AM25724, Be101914, AM25754, Be101914, AM25764, Be101914, AM25764, Be101914, AM25764, Be101914, Be101914, Be101914, AM27164, Be101914, AM24975, Be101914, AM27164, Be101914, Be101914, AM2716, Be101914, Be101914, AM2716, Be101914, AM2716, Be101914, Be101914, Be101914, AM2716, Be101914, Be1019 |
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| HEEAG23                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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|         |    |         |          |           | AP0005471, AC010530,7, AC020740,5, ALI65245,00, AC0054882, AL054372,33, AP0006891,<br>AC0574925, AL05364915, AC0060327, AL0497934, 2871961, AP0001401, AC0097431,<br>AP0003591, AP000081, AJ3573128, AL596582,9 AA525707, AA52584                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| НЕОМО63 | 8  | 603533  | 1 - 1322 | 15 - 1336 | BG026315, AW 102828, AI659843, BIES51400, AI640882, BIE208434, BPS10823, AN995547, BE169097, AA789122, AA925235, W44766, AJ86827, A002686, BE16708, AV62020, A1350733, AR0904052, AA252167, A003603, A1350734, AN09093, A1350734, AN09093, A135041, A1000803, A135944, AW086035, AA252680, AA252680, BF1694144, A1000803, A135944, AW085032, AA252808, BF170413, AA078243, BG112149, A135272, A165406, BF170712, AA078618, AA985450, AA25176, AU85776, BF26224, BF39222, AW386074, BG112215, AV662306, AA35715, AR520522, PE2085, AW19561), ANSE654, BG112217, AA01002, BG11215, AV662306, AA35715, AA109673, AA35715, AA109673, AA377683, AA3761150, BC0059941, AA109675, AA116676, AA3761150, BC0059941, AA109675, AA11667977, AA109672, AA3761150, BC0059941, AA109672, AA3761150, BC00599841, AA109672, AA3761150, BC0059941, AA109672, AA3761150, BC00599441, BC0059441, BC005941, BC00 |
| HEPAB80 | 98 | 1307790 | 1 - 785  | 15 - 799  | AW274007, AI677890, AW510786, AW468943, AA335322, AI807924, AW172560, AC006116.1, AC011506, 3.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| HFABG18 | 87 | 847073  | 1-1331   | 15 - 1345 | BEF5093, BEF80907, BE144166, AGNS9032, WGSTST, AMSTDT, AM645544, ANGS4800, BE507784, AMSTDT, A |
| нғавнуз | 88 | 566712  | 1 - 1333 | 15 - 1347 | EBRORSON, AMSTIST, AARSUTS, AZISTORA, 
| HFAEF57 | 68 | 534142  | 1 - 628  | 15 - 642  | AV655597, AW967329, AW963498, AV706016, AW966767, AL121984, 14.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HFCEB37 | 06 | 411345  | 1 - 788  | 15 - 802  | AW971191, BE710287, AA493766, D56115, H06701, Z41729, AA285136, AA256963, F04210,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| AL118652, AW893768, AW893769, AW160783, AF258348.1, AC007552.4, AL050152. 1. | AV699250, AV662248, AV699269, AV719565. | ALL 19979, BF34683, AYZG599, BF105390, AVISTA214, ALLI1971, PR920864, AWR88731, BR1683, AWL19979, BF346844, AAVZTSR14, AAZZS667, N32300, AW961610, BF976899, BF765872, BF1765750, BF765749, BF765443, BF75044, AAVZS814, AAVZS814, AYZZS18, R16237, BF34146, AAAD9492, AVYT3456, INT 100, AND00462, BF7047, AAACS814, AXACS814, AXYZS18, R16237, BF34146, AAAD9492, AVYT3416, INT 100, AND00462, BF34617, AAACS814, AVXS914, BF321, BF32112, BF3464, AVR9419, AVYT3416, BF3206, AVYT3164, BF321, BF3214, BF3214, AVSS914, BF3214, AVYT3409, AVXS914, AVXS914, AVXS914, BF3214, AVXS914, | AA44804, AA602540, AA719555, AC0189776, AC0220073, AC0188994, AC0075465, AC0074017, AB020872.1, AL053404.20, AL009181.1, AC06102.1, AC007686.5, AC007207.22, AC018808.4, AL109758.2, AL049759.10, AC007308.13, AC002301.1, AC007192. | HE 1956; R. A.H.)22-A.WOWSES, A.MOROSEA, A.MOROSE, A.R. MOROSEA, L. A.R. MAY ST. A. A.WOSTS. A. A. A. MOROSEA, A.R. MOROST, E. A.R. MAY ST. A. A.R. MOROST, A.R. MOROST, E. A.R. MOROST, E. A. MOROST, A.R. MOROST, A |
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|                                                                              | 15 - 470                                | 15 - 1881                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 15 - 1450                                                                                                                                                                                                                            | 15 - 541                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                              | 1 - 456                                 | 1 - 1867                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 - 1436                                                                                                                                                                                                                             | 1 - 527                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                              | 520369                                  | 513669                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1011487                                                                                                                                                                                                                              | 532060                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                              | 16                                      | 92                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 93                                                                                                                                                                                                                                   | 94                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 0.00                                                                         | HFFAD59                                 | HFGAD82                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HFIIN69                                                                                                                                                                                                                              | HFURIO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| AW779609, BF525663, AI380617, BF914419, AL079734, BG166965, AW069227, AL043351,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| A1267161, AV762870, AV658819, AV709273, AL042735, AAS03018, A1973173, AL046746,<br>  BF062357 A1963705 T69857 AV730245 BF810071 AW301736 - Z979871 - AC020913 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AL031281.6, AC007637.9, AL096757.1, Z93017.6, AC087225.1, Z83840.7, AC008073.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AF245699.1, AC010349.7, AC087315.21, AL163011.3, AC004106.1, AC004132.1, AC008925.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC004990.1, AL133351.33, AC010618.7, AC006275.1, AL035405.10, AC034203.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC006930.1, AF156495.1, AC008754.8, AP001732.1, AL139824.22, AC003037.1, AP001646.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| ACU05102.1, AL030341.18, AL034420.16, AC024073.4, AL117362.28, AC008521.5, AC008521.5, AC008521.5, AC008521.5, AC008521.5, AC008521.5, AC08521.5, AC08521. |
| AL049569.13, AL109914.16, Z95152.1, AL163541.13, AC006367.3, AL442203.12, AC005684.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL117377.18, AL109828.22, AL031681.16, AC007488.15, AC007425.16, AC018462.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| AC007934.7, AL078602.13, AC010002.6, AC005038.5, AC009743.1, AC006538.1, AC053467.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Z95115.1, AP001922.4, AC010203.13, AC010150.3, AC006545.3, AC006546.9, AC004970.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AP001696.1, AL390736.6, AC003035.1, AL355543.13, AC007318.4, AC007381.3, AC006253.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC022173.7, AC040160.4, AC003684.1, AC009331.5, AL109823.23, AL451107.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AL359873.11, AC004605.1, AL035682.16, AP002453.3, AC063947.30, AC006270.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AC016526.6, AC003664.1, AL078634.24, AL157897.7, AL009031.1, AL137802.7, AJ251973.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC002326.1, AL356421.10, AC006388.3, AC078846.2, AL138721.16, AC004103.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC090949.1, AC090944.1, AL139150.12, AL162423.18, AP001718.1, AL109915.10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AL390208.17, AC004616.1, AP002851.2, AC017100.4, AC022425.6, AC006080.1, AC005027.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC017006.4, AC024163.2, AL049540.11, AC005522.2, AP000353.2, AC008008.2, AL445205.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC078843.2, AC073864.28, AL161657.22, AL031280.6, AL035696.14, Z81364.1, AL157938.22,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC090426.1, AL389883.9, AL024474.1, AL138703.10, AC008266.3, AC073057.6, AL132800.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC007784.7, AC002996.1, AL354816.5, AC011449.6, AP000193.1, AL022313.1, AC008379.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AP003355.2, AC005004.3, AC005514.1, AL118501.22, AL009028.1, Z86064.1, AP002812.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AL035249.6, AC009131.6, AC002549.1, AC032011.14, AL109984.14, AF001549.1, Z84467.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL034419.22, AL512883.5, AC006204.1, AL353574.8, AC006960.1, AC009079.4, AC009503.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| D87009.1, AL354932.26, AC005014.1, AC005859.1, AL139110.17, AC003662.2, AL035089.21,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC005751.1, AL390738.4, AL133246.2, AP000699.1, AC020659.5, AL133355.12, AC004854.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL359236.4, AC006237.1, AK023233.1, Z85999.1, AL022323.7, AC003046.3, AL031730.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL160471.5, AL160071.16, AC010548, Z82206.1, AF029308.1, AC005498.1, AL133342.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AP000348.1, AC011465.4, AC004812.1, AC007221.2, AL022316.2, AL035072.16, Z97630.11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AL023883.6, AP001150.4, AL109825.23, AL137782.9, AL096800.20, AF252279.1, AC005695.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC016993.4, AC007620.30, AL022237.1, AC006481.3, AC018812.5, AL035420.15,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC004611.1, Z84487.2, AC018719.4, AC010163.7, AL133344.28, AC011290.3, AC007292.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| ACU11895.4, APOU1929.4, 003/21.1, ACO02552.1, ACU11444.5, ACO05527.1, AL4510/3.13,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|                                                                                      | 15 - 795<br>15 - 762<br>15 - 1103<br>15 - 1873<br>15 - 1873<br>15 - 1873<br>15 - 1873 | 1-781 15-795<br>1-748 15-762<br>1-1619 15-1103<br>1-1879 15-1873<br>1-1370 15-1873<br>1-931 15-945 | AC0045951, AL13879219, AJ451185.14, AC002470.17, AL008732.1, AC006460.3, AL137119.26, AC006786.1, AC06621.1., AF134726.1, AC01020.5, U52112.1, AC007597.3, AC01040.21, AC00215.1, AC00757.3,  BE22940, A479528, AW242860, R46796, M63053, AI017670, BE049467, A1671740, AW001738, AA80191, AM201731, AM2019581, AM2017401, AW0074901, AP0171051, AP01710 | ALS29436, BG254023, AA069656, AW512689, AA928735, BE901109, ALS29437, BE074967, | BE074973, AA423996, AI027673, AI130940, AA827360, AA424006, AA421599, AW602733, | A1580837, AL526924, AA114876, AA576953, A1858981, BF222157, AL526960, BF542049, AA156831, a 1200715, A138322, A 088755, AW602730, A 187021, A1 527000, H10340, A1400041, H10044 | AA252300, AA188494, AA856927, R44331, AA588683, AW364266, BE092940, BE007334, R51006. | AI253378, AA481649, AI686745, AI628242, BE092920, BF733881, AA729977, BF026424, AW804569, | AA421594, AW994967, AA481416, BE73257, BF876214, AA679567, AW028221, AUI34538, | BE251492, BE729280, AI906091, BC002480.1, AK023414.1, AP002347. 3. |           | AW118870, BE044339, AA426363, AV730822, AI868197, BF947599, AA927228, BF952754, | BF952302, BF952504, AW905268, AW905266, BF952591, AI673798, BF952850, BF952505, | AW905263, BF952750, BF952589, BF952851, BF952752, AA897687, BF572515, AW905328, | BE699539, AI830527, BF952755, BF210822, AA431528, AA029326, H41714, AA437157, N53641, | BE699547, AW905379, BE699537, BE796741, AW898982, AI218421, AF289076.2, AC067967. |         | AV662272, AV725496, AV727824, AV699218, AV719825, AV719156, AV699200, AW952432, | ` |         | AC004491.1, AC024579.4, AL136084.11, AC016564.5, AC005015.2, AC007011. 1. | AA483223, AA552843, AV762050, BF991286, AA623002, BF827410, AW193265, AI434706, | AV759204, BE350475, AI270117, AV760937, BF217299, AV710066, AA610493, AI350211, AL041690, | BF475381, AV764241, AV764307, AW673241, AV762139, AI192631, AA552856, AV763540, | BF676536, AA468131, AV682003, AI368256, AI345157, AA649705, AI345518, AV760774, AA480772, | AA521323, AI538433, AA644538, AL037683, AA577906, AA613227, AA503475, AW270382, | AI355206, AW021583, AV759274, AA521399, AV761155, AA492166, AV735495, AI431303, | AA490183, AW088846, AF330238, AA857486, AA493621, AV759382, AW438643, AA579362, | AI610159, AA525790, AA507824, AV742057, AV763255, W60061, AV761786, AA644551, AI254615, | AV 1353 /U, AW 6 126 / 0, AAO 490 444, AAO 520 51, AAY 64 1/00, AAS 19 130, AAO 629 12, AAS 250 54, AW 718583 AW 977303 AAA 710 640 A 1043 770 AV 734664 AV 740 674 AV 750 670 713 | A A ADDRAGY STILL STATEMENT A A A A A STATEMENT A A A A A A A STATEMENT A A A A A A A A A A A A A A A A A A A |
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| 545726 1-1089<br>545726 1-1089<br>778070 1-1619<br>701988 1-1370<br>634161 1-931     | 545726<br>545726<br>545726<br>778070<br>778070<br>609826<br>701988<br>634161          |                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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                                         | ř.        |                                                                                 |                                                                                 |                                                                                 |                                                                                       |                                                                                   | 86      |                                                                                 |   | 66      | 100                                                                       | 101                                                                             |                                                                                           |                                                                                 |                                                                                           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| AMDY499, AAC806, AAH1210, AAC84651, AAC84724, AAC8449, BF00152, AAD9321, AAD5113, AAU15549, AAC806, AAH16206, AAU16206, AAU16206, AAU16206, AAU16206, AAU16206, AAU16205, AAU162205, AAU16205, AAU16 | ANWOSKOG, ANYOSKOG, ANKOSKOG, ANGORGO, ANGO, ANGORGO, ANGO, ANGORGO, ANGORGO, ANGORGO, ANGORGO, ANGORGO, ANGORGO, ANGORG | AUII8319, AUII8145, AA001321, AZ68416, AUI44910, AA004368, AW291988, AUI44790,<br>AA677418, AUI56615, BE70844, AA010 908, AA707413, AA009391, AA004366, AA122399,<br>BG000061, AA1584, AA878867, AV065708, AA152372, AZ127949, R2047, EAS288, AA346924, 197751, 179858, AA15288, AA346924, 197751, 179788, AZ12488, AA346924, 187751, 179788, AZ12458, AA8839578, AK0249221, AK02161. 1. | ALE30986, AJUSTAS, BIESOFE, LABHSH 43, AUGHO BEFORSH, AJUSHGA, DASUS-200, ALOSROG, AMUZDAR, ALOSHOG, ALOSHOG, ALOSHOG, AND ASSERVEN AND ASSERVEN BENEAR AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSERVEN AND ASSER |
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|          |     |        |          |           | AC007566.2, AC011465.4, AC005540.4, AC025572.13, AP001713.1, AC002352.1, AC007193.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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|          |     |        |          |           | AL139092.12, AF001549.1, AL121865.7, AC010458.5, AL121895.26, AL133415.12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|          |     |        |          |           | AL121657.2, AL389921.12, AP000100.1, AL031727.42, AL161747.5, AC008395.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|          |     |        |          |           | AL353140.12, AC073593.13, AL157828.14, AL157398.6, AC079141.7, AC006952.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|          |     |        |          |           | AL034431.16, AC078962.30, AC008882.6, AC009228.4, AP001694.1, AL121899.37,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|          |     |        |          |           | AC005697.1, AL160273.9, AL031291.3, AC008745.6, AL137859.3, AL161896.16, AC007055.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|          |     |        |          |           | AL121910.26, AL117328.5, AL450169.1, AC005768.17, AP000208.1, AP000130.1, AC005071.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|          |     |        |          |           | D83989.1, AP002008.5, AP000247.1, AL353613.10, U95740.1, AC002045.1, AC006057.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|          |     |        |          |           | AC0093144, AC008747.5, AF279660.2, AC004231.1, AC078961.23, AP001725.1, AL035089.21,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|          |     |        |          |           | AP003357.2, AJ003147.1, AL359739.8, AL352984.4, M55538.2, AC005304.1, AC079045.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|          |     |        |          |           | AC004522.1, AF241728.1, AC007221.2, AL161937.13, Z82097.1, AF069291.1, AL110114.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|          |     |        |          |           | AC008482.5, AL109615.41, AL391122.9, AC018618.5, AL161421.11, AL049869.6, AC010489.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|          |     |        |          |           | AC005007.1, AC083870.2, AC006285.11, AL158035.14, AC007198.6, AC078876.15,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|          |     |        |          |           | AF243527.1, AL391280.15, AL031681.16, AC016025.12, AL160410.24, AL138762.20,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|          |     |        |          |           | U93305.1, AL031985.10, AL121754.18, AC008394.3, AC007161.1, AL590732.7, AC022212.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|          |     |        |          |           | AP002851.2, AL356321.9, AL008708.4, AL359846.11, AC006270.1, AL050349.27,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|          |     |        |          |           | AL445483.13, AC005325.1, AL353748.13, AC009955.4, AC002381.1, AL122004.17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|          |     |        |          |           | AC009230.3, AL049776.3, AP001710.1, AC008547.5, AC008555.5, AC005520.2, AC002565.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|          |     |        |          |           | AL031176.8, AL138741.13, AC005678.1, AC004590.1, AL133551.13, AC009238.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|          |     |        |          |           | AC007673.7, AC008872.5, AJ289880.1, AL096793.20, Z85987.13, U57009.1, AC004890.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|          |     |        |          |           | AC005822.1, AL590762.1, AL160237.4, AL391684.6, U91326.1, AC083875.1, U96629.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|          |     |        |          |           | AP000426.3, AC013429.12, Z98051.6, AL031055.1, AL049758.11, AC004826.3, AL355096.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|          |     |        |          |           | AC009309.4, AP001830.4, AC008755.6, AC007749.3, AC005887.3, AC002395.1, AC002418.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|          |     |        |          |           | AC010504.7, AL161627.13, AL118511.25, AL1139317.5, AL442203.12, AC004386.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|          |     |        |          |           | AP001972.4, AC016830.5, AC004832.3, AP001614.1, AC004846.2, AL035685.21, AC005701.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|          |     |        |          |           | AL132713.11, AC007465.4, AC005669.1, AL352976.3, AF134726.1, AC006052.5, AL133328.13,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|          |     |        |          |           | AC079684.16, AC011739.7, AC016027.15, AL359851.19, AC078958.30, AC022173.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|          |     |        |          |           | AC011359.5, AC006026.2, U57007.1, AL139100.9, AL445675.9, AL445258.4, AC009470.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|          |     |        |          |           | ALI33324.13, 282194.1, U18391.1, AC002316.1, U18394.1, AL356801.5, X54176.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|          |     |        |          |           | AP001/814, AL13590/21, AL553/34;12, AL03196340, AL133338, AL135/44;4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|          |     |        |          |           | ALIZI601.13, AL559813.23, AP000036.1, AC009464.7, AC004812.1, AC018710.4, AL160192.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|          |     |        |          |           | AC026463.4, AL109825.23, AL121902.13, AC019041.8, AC079602. 15.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HHENV10  | 106 | 562772 | 1 - 1141 | 15-1155   | AC004912.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| HHFFJ48  | 107 | 634521 | 1 - 2552 | 15 - 2566 | BF872051, BF760479, AA486028, AI536141, N91095, AW301931, BF772459, AW852705, AW852684,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|          |     |        |          |           | AW852657, BE138714, AB058744.1, AL589723.7, AC006512.12, AL451107.6, U47924.1, At 500762.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| COLLEGIA | 100 | 411000 | 1 (17    | 100 31    | A A SOUTH A STREET A A SOUTH A A SOUTH A STREET A A SOUTH A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET A STREET |
| HHFHJS9  | 108 | 411332 | 1 - 64/  | 199 - 61  | AA833//U, AW8//42b, AA804902.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| 722,<br>25, AV756848,<br>22, AW303196,<br>2795,<br>3466,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 77, A1311505,<br>AW238583,<br>593,<br>AL096840.25,<br>AL133163.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | AJ400877.1,<br>AJ45483.13,<br>AL445483.13,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ALI379211, AL035853, AC004815.2, AL1384912, AC011446, AL035875, AC003922, AL04976111, AC09416612, U950901, AC010507, AC00005216, AC0103197, AL13937617, AC007544, AL15621420, AC084862, AC0167728, AC0163862, AC0089466, AC0047552, AC0073863, U912111, AL0497763, AC01650892, AC0117423, AC0188084,               | AC004148.1,<br>AC008622.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | AC011465.4,<br>7,<br>AC021016.4,<br>0,<br>AC005015.2,<br>AC034193.4                                                                                                                                                                                                                                                                                                                                                                                                                                                   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| 93428, AV738;<br>56074, AV7121;<br>60395, AI61203<br>E252421, AU15<br>A1251576, AI58                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 04480, AF0746<br>60, BF673630,<br>99745, AW961<br>AL139100.9,<br>AC016587.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | AP001/16.1, A<br>AC004983.2,<br>AC006285.11<br>5, AL139316.5<br>AC007256.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | AC020915.6,<br>1, AC009060.<br>AC011484.4,<br>AC004019.2<br>AC005288.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | AC007421.13<br>AC007421.13<br>AC007421.12<br>AF107885.2,<br>AP003357.2,<br>ALS12378.7,                                                                                                                                                                                                                                                                                                                                                                                 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| BE409452, BF7<br>M254798, AV7:<br>M890348, AV7:<br>AW021917, BI<br>2, BG249643, AV,<br>AL048255, AV,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | A1251250, AW5<br>F337291, H986<br>F325535, AW4<br>AC005368.1,<br>AL034372.33,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | AC019205.4,<br>AP001726.1,<br>AL022326.1,<br>AL139809.16<br>AC018711.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2, AC011446.6<br>AC000052.16,<br>AC016772.8,<br>C005089.2, AV                                                                                                                                                                                                                                                      | 5, AC003291.1,<br>5, AC003070.1<br>AL035458.35<br>AC009501.3,<br>AL135978.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | AP001/28.1,<br>2, AL049539.2<br>AC007766.1,<br>0, AL031005.1<br>AC006064.9,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | AC015982.9,<br>AL050349.27,<br>AC022392.4,<br>AC018758.2,<br>AC007308.13,<br>AC009570.13,                                                                                                                                                                                                                                                                                                                                                                              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| AAJAGASAA (ARIGHA) KAAGASA HARIATA HARBASA HARIAGASA HIPGAJASA ANTSAYZA ANTANTANA ANTANGAA (ARIGHA) KAAGASA HARIAGA ANTANGAA ANTA | ADZ224184, AA747803, NYSO4104, A1349748, A175238, ADZ21526, ANSO4489, ADG704677, ADII 1505, AMIG6864, AA744001, AIGIGGG, ARBOLZ6, AA57292, IR3237291, 119866, IR675630, AW233853, AMBS756, AA46901, IRF917533, ALI 158455, AJS96222, IR732355, AW499745, AN961593, ARW023473, AGG141756, ACGH41036, ACGW62312, ACG053661, ALI 150701943, ACGW67606, ALI 12727865, ALI 1537733, ACGW65877, ALI 133165, ACGW67606, ACGW67621, ACGW67676, ACGW67606, ACGW67621, ACGW67677, ACGW67606, ACGW67621, ACGW67606, ACGW67 | ALUSSITII, ASSELIA, AUGUSSA, ALUGUSSA, AUGUSSA, APUGUSTA, ATLINESA, ATACOWGNILIA, ACOMGNEZ, ACONGSESO, APUGUSZA, ACONGNEZ, ACO | ALI3792.11, AL038639, AC0048152, AL138699,12, AC011446, AL0358575, AC0039821, AL4649761.11, AC09416.12, U95901, AC0105307, AC0005216, AC0103197, AL139376,17, AC097478, AL386142.10, AC0844662, AF534821, AC0107328, AC0383662, AC008346, AC0047552, AC0073863, U913211, AL0497763, AC0060892, AC011723, AC018088, | ACOMPSTAL, ALBOHOMS, ACOMPSTAL, A | ACOURTS-3, ALOZOFRI-4, ALGORD-ST. ALLOS-ST. D. ALOROSTOS. I. ACOURTS. I. ACOURTS. AC | AC0063293, AC0064823, AC0731833, ALI62426.20, AC0159829, AL355748.13, AC0063291, AC0168311, AC008447, AC0708782, ALI63649273, AC0064411.3, AC0168311, AC008294, AL13782.15, AC027382, AC0074211.2, AC0074211.2, AC007686.5, AP001381.1, AC08788.2, AF107885.2, AC004781.3, AL162644, AC0182833, AC0079183, AC007886.4, AC009731.3, AC007881.3, AC00788 |
| 43123, Al6484<br>99358, Al61215<br>54881, Al28488<br>25431, Al3062<br>744242, AW27 <sup>2</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 04104, AI3497<br>0603, AI801200<br>17533, AL13849<br>AC004150.8,<br>AC008760.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | AC005280.3,<br>1, AC004965.2,<br>AC011464.5,<br>2, AC005701.1<br>AC073657.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ), AC004815.2<br>12, U95090.1,<br>), AC084865.2<br>U91321.1, A                                                                                                                                                                                                                                                     | AC008440.8,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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| AW063936, AI3<br>AI284640, BEL:<br>W965518, AI28<br>W301350, AV7<br>AW274191, BE<br>F980463, BF24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | A747889, AW5<br>A744001, AI61<br>A496901, BF91<br>AC011475.6,<br>AC007314.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1, Z83826.12,<br>AL096701.12<br>AC006480.3,<br>AC007664.12,<br>AC005052.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1, AL035683.9<br>1, AC004166.1<br>, AL356214.20<br>, AC007386.3,                                                                                                                                                                                                                                                   | AC009060.<br>AL360169.17<br>8, AC007374.6<br>AL450226.1,<br>AL022336.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| AA363260, AV740060, AV740060, AV740060, AV74061313, AV710482, AV71 | AI224184, A<br>AI064864, A<br>AI053786, A<br>AP002347.3,<br>AF196969.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | AC090939.1<br>AC090939.1<br>AC022476.2<br>AC004638.1<br>AC021999.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 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| ACO06211, AC008802, ALISTOSER, AC006404, AC0114423, AC01181142, AC0025531, AC012306.11, ALISTOSER, ALISTOSER, AC0065513, ALISTOSER, ALISTOSER, AC0072162, ALISTOSER, AC0072162, ALISTOSER, AC0072162, ALISTOSER, AC0072162, ALISTOSER, AC0072162, ALISTOSER, AC0072161, | MW24897, IRPS2801, IRPS2804, A1675194, AW02B119, IRPS2767, BFR27050, AW425801, AR09952, IRPS2804, AW450497, ATTOPRS6, AA595164, A108096, AW612404, IBP92735, AW09092, IRPG3826, AW617134, AA645065, AA580017, AR180005, AR86061, AX66061, AA655784, AW09052, AR89011, AW32516, AC52906, AW52853, AD6494, AC670745, AA565786, AA52666, AC67526, AA52606, AW751864, AA52666, AC675210, AC67506, AC67521, AC67521, AC67804, | ALGSBIG, BGZ3074, BFS0806, BFBSSSR2, AA23420, APV26432, A112924, AV293770, AA48823, R101942, AV293770, AA48823, RR1805, AV338445, AVV62429, AP01235, AV316552, AA454665, A4459366, BE39916, BFRS6601, R4559, AR69663, A1080203, BFBS6601, A10802324, AN065282, BOZ22935, FILIT, ARV99131, AA46866, AW029153, AA568855, A1123718, A1352145, AA234190, BCZ51585, A4459970, R41441. | AB99020, Ad80056, AW300615, AW300620, AIS80129, BE386428, BF920454, BE386547,<br>AW90818, AP911546, AV702666, AJ80121, AJ408227, AV725146, AW901919, BE967591, H41544,<br>AA236679, AA438031, Ad22476, AA9122386, JA23129, BC004271. I. | BE905356, MU26821, AA509776, BF114724, A1435527, AL136946, AN0498357, BF240622, AA969442,<br>AIT67392, AI142574, A1094514, AV073866, AW241144, AA206695, AA040034, AA354909,<br>AWW72134, AA811456, AA953895, AA0406838, C01416, AA445720, AL138875, B, AY027525, 1. | AMAILT23. BRODOG, MISSA, NERODE DRENDER, ARREDSTS, ALSTSOR, AND MITT, BRODOG, MISSA, MARCE DRENDER, ALGORITA SECTION ALGORITAL SECTION ALGORITAL BESTATEMENT OF ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITAL SECTION ALGORITATION ALGORITATI |
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| BE886728, AW827106, BE527014, A1313352, BG110517, AL039086, AW079336, AL251434, A1274728, BE868028, A1524780, A188047, A188047, A188047, A188047, A188047, A188047, A188047, A188047, A188047, A188048, A188048, A188047, A188048, A |
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| AL036925, A1345258, A1922638, A1470651, AL036857, AW050578, AW196105, AV682227, A1306705,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AW269097, AI620639, AI611348, AW090393, AL042628, AW152469, AA833760, BG256090,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| A1866798, AW074993, A1567351, A1431424, A13416414, A1311604, AW105601, BE966990, AL044207,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AW167918, AI611738, AW169604, AW268253, AI862144, AI567612, BE886827, BF793308, AI890806,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| A1349256, AL036664, A1554821, A1312152, A1955906, A1336495, BF970768, BF885000, AW075084,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL120854, BE895585, Al950664, BE897632, BE964078, BF872670, AW022699, Al349937, AL036923,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AW089572, AI334884, AI307543, AW151138, AW071412, BF885081, AI307708, AI312325, AI500659,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AI868204, AI340659, BF816037, AI280655, AI612885, BF092710, AW302965, BF339322, AI334930,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AI309443, AV699211, AV734185, AI307520, AI445237, AV724373, AI590423, AV756798, AI345739,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AI889168, AI440263, AW117743, AI312143, AW673635, AW806761, AI343037, AV708834, AI434256,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AI312428, W33163, BG109270, BE966829, AI349955, AW075093, AI371228, BE548914, AW827206,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AI348897, AA427700, AI306613, AI312357, AI335426, AI348777, AI308032, AI569583, AI687127,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| BG249582, AI783997, BG030364, BG104820, AW161579, AI627988, AI344785, BG113662, BE971716,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| BF970449, AL079963, AL036718, BE047852, BE785868, AI207454, AI382670, AW020095, AI874166,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL036901, BE047952, AI670009, BG180996, BF970990, BF526262, BG027280, AL036274, BF061286,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| A1497733, AL041150, A1288285, A1890507, BG026428, AW827115, AW268964, A1343091, A1318280,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AI567582, BG165051, AI554245, BE963035, BE138658, BG260037, AI310582, BG032208, BF344691,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| BE885490, AF352730.1, AF205952.1, AF323081.1, AK024538.1, X53587.1, AL512765.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AL050393.1, AK025254.1, AF090901.1, AK026542.1, AL136787.1, AK026597.1, BC006525.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| AK026855.1, AL122110.1, BC008780.1, AF090943.1, AL133098.1, AL136799.1, BC008070.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC003687.1, AK024524.1, AF091084.1, AL049466.1, AK025967.1, AK026480.1, BC002839.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC006807.1, AL136789.1, AL157482.1, AL117394.1, AK025391.1, AL137560.1, AY034001.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AK025349.1, AF125948.1, AL359615.1, AJ242859.1, AK025906.1, AL136915.1, AL110221.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL050092.1, AL512718.1, AB056427.1, AK027146.1, AB060825.1, AL133075.1, AK025484.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AK000391.1, AF056191.1, AB051158.1, AK026583.1, AB060908.1, AL133557.1, AL117457.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| AF217987.1, AK026452.1, U42766.1, AL133606.1, AK026534.1, AL133067.1, AK024588.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AB047615.1, AB048954.1, AK027182.1, AL049464.1, AL133113.1, AL133560.1, AL137521.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| BC008983.1, AB060912.1, AF097996.1, AK026353.1, BC008899.1, BC001967.1, AK026959.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL137459.1, AB060839.1, BC003548.1, AF090900.1, AL050116.1, AB052200.1, AL133016.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL359620.1, AB060214.1, AF057300.1, AF057299.1, X72889.1, AK000618.1, BC002643.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| BC008417.1, AK026164.1, AK026506.1, AK026741.1, AL359618.1, AL442082.1, BC007199.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AK025465.1, U91329.1, L19437.2, AL049314.1, AB056421.1, BC004958.1, AK027164.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AB056809.1, AL162062.1, AL050149.1, AL389982.1, AL137463.1, AL122123.1, AF230496.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| BG239882, BG257535, AW152409, AR612885, AW022682, AW148120, AL569579, AL52023, AR608956, AW07514, AR61201, AR608956, AW07514, AR61201, AR608956, AW07514, AR61201, AR61201, AR61201, AR61201, BG10684, BE880900, BG106854, AW28623, AW12010, AL580296, AR5544, AR1026664, AR072507, BE880702, AR163752, AR075207, AR75474, AR075207, AR075207, BE880702, AR075207, BE880702, AR075207, BE880702, AR075207, BE880702, AR075207, BE880702, AR075207, BE880702, AR075207, AR075207, AR075207, AR075207, AR075207, AR075207, AR075207, AR080106, AL580204, AR08864, AR13204, AR075207, AR075207, AR080106, AL580204, AR080106, AR080206, AR080106, AR15206, AR080107, AR080106, AR080206, AR080106, AR15202, AR15 |
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| AB47801, AB653031, AB6608871, AL3596151, AR0006181, AL1375501, AF224441, AL359504, AL1175831, AK126647, AL1330801, AK1175831, AK126647, AK1139001, AK1266031, AK1175831, AK1266481, AK113411, BC0071091, SG19531, AK10760431, AR0600081                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AL135571, AL136781, AB497581, AL1220931, AL336661, BC008933, AR026922, BC008321, AR026921, BC008341, AK026331, AB6535661, AL0361941, AL13961, AL4420821, AL10221, BC008361, AL173941, ANB611881, AL3899221, AL1142571, AK026941, AK029021, AL1220981, AL0601161, AK025771, AL0801241, AL1267991, BC0056631, AK029021, AL1220981, AL0901161, AK0257721, AL0801241, AL1267991, BC0056831, AL122041,  |
| AK026542.1, AK000647.1, AB060863.1, AL110221.1, AL137527.1, AB063070.1, AF218014.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| 1-1128 | 15 - 1142 | ALDOSTIAI, BOUOTSTSI, MACRORORSI, ALISTSSIR, BUGORSSII, ALGAUTZI, BUGORIZI,<br>AROGESIAI, ATOPREALI, AND HOST, ALISOSKI, XESJAII, ARDOTSOGI, ALGAUSTOS,<br>AROGENIA, ALBOTSOS, AND HOSTORIA, AROZESOZI, AROGESIAI, AROG | ALL BORGH, ANJ-LOSCH, ALL BOSSEN, ARDONOLH, ANJ-LISTH, ALMOROGUL, ARGES/1971, ARGUSGORG, | ALZ 18848 BED7844, BED7985, MOSTAN, ALS 18844, BED4844, BED7945, MOSTAN, ALS 18844, BED78444, BED7945, MOSTAN, ALS 18844, BED7945, ALS 18747, A |
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|        | 876571    | ALU4<br>AK05<br>AK05<br>AR02<br>AK12<br>AK02<br>AK02<br>AK02<br>AK03<br>AK13<br>AL13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| HKGDL36 | 125 87 | 877489 | 1-1038 | 15 - 1052 | ARBORSO, AMARONS, ARROROUS, AGRIGATOR, ARROSEZA, ARROSEZ |
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|         |        |        |        |           | Wittosist, AASHYDI, BI 1917412, BI 1927406, BI 191748, AWNSEGOS, AWRODESS, AWNSEGS,  |

| BE613727, BE880341, BF814360, AW005029, BF921092, AV712606, AV681927, BE967251,                                                                                                      |
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| BE904021, A1806/41, AWU39/115, BG108334, BE33637/, BF929383, AL234/34, BF704338, AA824313, AWU83804, AIS39462, BF129016, AI446605, ALS13741, AA830821, BE966699, AJ924035, AJ445976. |
| BE875966, A1242248, BE885353, BE538466, A1620093, A1537643, A1358042, BE880697, A1683255,                                                                                            |
| AIS91412, AIS91081, W81248, AIS36910, BE964962, AW834325, AI864827, BE048026, AI872159,                                                                                              |
| BE061389, BE964767, AI591057, AW073868, AI863256, AI690449, BE907440, AI884574, F35927,                                                                                              |
| BES78032, BE965121, N95566, AV743128, AV706465, AI445588, BE899377, AI934000, AI280670,                                                                                              |
| AI583578, AI627714, AI500039, AV708075, BI5900603, BF752858, AW265004, AI623682, BF341610,                                                                                           |
| AW079032, AI925736, AI252077, AI590787, AW025533, AI267185, BG105895, BE964600, AL513789,   E26535 at 148877 B1965527 B1967755 B1964700 aW046864 at 514167 at627880 BE621140         |
| AV710267, AI678302, AI926878, BI878028, AI633300, BF817402, BF753053, BE875407, BF722999,                                                                                            |
| A1689614, A1624668, BE966390, A1811192, A1866002, F28295, BG260275, BE963286, BF753056,                                                                                              |
| BC002851.1, AF181562.1, AF196971.1, AJ012582.1, BC003104.1, BC007248.1, BC001470.1,                                                                                                  |
| AF230402.1, BC002948.1, AF352728.1, U77594.1, AK000212.1, AB063077.1, BC003687.1,                                                                                                    |
| BC004314.1, AK026865.1, AK025491.1, BC001294.1, AB060908.1, AK025906.1, AL137557.1,                                                                                                  |
| AL136752.1, AK000598.1, AL121656.2, BC002816.1, BC002356.1, AJ010277.1, BC002397.1,                                                                                                  |
| BC004529.1, AL157464.1, BC000785.1, BC000725.1, X95876.1, AB060832.1, BC004324.1,                                                                                                    |
| BC002777.1,                                                                                                                                                                          |
| AK026164.1,                                                                                                                                                                          |
| BC001969.1,                                                                                                                                                                          |
| BC005890.1,                                                                                                                                                                          |
| AL136799.1,                                                                                                                                                                          |
| AL049460.1,                                                                                                                                                                          |
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| BC001349.1, AL137459.1, BC004195.1, AL512718.1, BC001963.1, AF111847.1, AB060914.1,                                                                                                  |
| AL353935.1, AL136766.1, AK026600.1, BC002491.1, BC000778.1, AL096720.1, AL359622.1,                                                                                                  |
| AL049314.1, AB047941.1, AK025119.1, BC004333.1, AF205861.1, AL133588.1, AL136586.1,                                                                                                  |
| M92439.1, AL136790.1, AL117648.1, AL137657.1, AF069506.1, BC007207.1, AL133081.1,                                                                                                    |
| BC004202.1, BC005931.1, AB060839.1, AL080137.1, AB056768.1, M79462.1, AK025410.1,                                                                                                    |
| AL390167.1, AK026533.1, AF090934.1, BC003052.1, BC005151.1, BC000217.1, BC008488.1,                                                                                                  |
| AL162062.1, BC004131.1, AL136842.1, BC009294.1, AB019565.1, BC000348.1, AK024594.1,                                                                                                  |
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| AL353625.5, BC002911.1, X66975.1, AK024570.1, AK000450.1, BC008070.1, AK024533.1,                                                                                                    |
| AB048888.1, AK000432.1, AL133645.1, BC004899.1, AL359596.1, BC002535.1, AK026741.1,                                                                                                  |
| BC004383.1, AF271781.1, AL117585.1, AB04547.1, AB063079.1, AK000310.1, AF036268.1,                                                                                                   |
| AB049758.1, AL080074.1, AL442082.1, U42766.1, BC004926.1, BC004960.1, BC005872.1,                                                                                                    |

| AMD09391, ATS8291, ARODSOMG, ROUGHSON, BADGYST, IRCODYST, BCONFG41, AND05361, AD060929, ARODSOMG, ROUGHSON, BADGYST, BCONFG41, AND05361, | RATOSTS, AMSTATA, AMORONS, BIRCTS, AMSEGOS, WASSISS, AMSTAGORS, AMSTAGORA, AM |
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| MIJERSOS, A, COROSTAG, A, COPOSAG, A, DEBOSAGO, A, COROGO, T. I. AMBEGILLA, APRORESSA, A, COROGASO, CA, ALLISSONIO, MAISSONIO, MAISSONIO, A, ALLISSONIO, A, ALLISSONIO, A, ALLISSONIO, A, ALLISSONIO, A, ALLISSONIO, A, ALLISSONIO, A, COROGASO, A, ALLISONIO, A, COROGASO, A, COROGASO, A, ALLISONIO, A, CAUGASO, A, COROGASO, A, COROGAS | ALZ.5996, BERGHZ, DE RESTAGE, AVAIOLS, ARRELLS, BERGZOZ, BERGGOZ, ALGOZ, ALGOZ, ARGOZ, ALGOZ, ALG | BERSH 619, A U133975, AWI 70191, AVIZ2948, RG (19805), AWG 
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| AA.298600, AA.21314, HEROOD, EASSAG, AAAHON, RA, AASSEG, AATTG420, REV.2122, BEYSZTZ, PEPDZA, 117922, AA946813, AAASSEG, BEYSZYS, AAASSEL, AWSSEQ, ABLSZOG, AAZSEGO, AAASSEGO, AASSEGO, AAASSEGO, AASSEGO,  BG256275, BB867624, BB907396, BB855521, BF034422, BF530803, AW959247, BE782005, AI126689, ALL21446, AA737065, AW640129, BFR6803, BE746763, AA2016154, AA460401, AI276330, BF998689, AA4295243, BE242721, BG035901, AL040350, BE242810, T86168, BF983867, W05088, AAA4734, AI133402, AR064093. 1. | AA35004, AC0187974, AF224669.1, AF28321.1, AC0078833, AC0060382, AC03425.1.5, AC006454, AC008149.14, AL355392.7, AC0060575, AC084864, AL354720.14, AC0084865.2, AC006438.7, AC | AL5.89de, BP97544, BC260893, BP629do, AW25089, AW954519, BG118275, AG63556, Ad19205, Ad63556, Ad63556, Ad63566, BE646174, Ad970513, AW302235, Ad619197, AR2566, AH79026, AIG5567, AIG1206, AIG61905, AIG1206, AIG1206, AIG1206, AIG1206, AIG1206, AIG1206, AIG1206, AIG1207, AIG1208, AIG1207, AIG1206, AIG1207, AIG1206, AIG1207, AIG1 | HEIGHSHAM, IRF72639, AUSHJOY, ALIQS33, AGSS9494, AJ786628, AAA163005, AGBG413, AWJ77205, BIG16533, A1199015, AA440235, NG1293, AL689890, AL6870764, AA705532, IB0033, H5017, T99745, HTR217, R8019, LB0995, AA40598, AA3098, NT5468, H42449, BE766738, AM153531, AA707662, AA786220, BE766726, AR69599, AA3098, NT5468, H4244, M2529, AA407662, AA786220, BE766726, BR8303, P4946, BR83040, AW971740, A4432644, AA41120, AA41132, AA41131, AA41332, AA41332, AA413333, AA43324, AA43324, AA43362, AA43624, 
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                                               | 740755                                                                                                                                                                                                                                                                                           | 684216                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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                                               | нгропл9                                                                                                                                                                                                                                                                                          | HLHAL68                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| BE672640, AW129223, AL042931, BE672622, BE672627, AI492510, AL042729, AL042832, AL047611, BE6727254, BE672626, AL043295, AL337075.17, AP0648341, AL133082. 1. | AV655891, AV718605, AV690404, AV719284, AA923549, AI950351, AV656411, AV720179, AV654765, AV656119, AV697855, BF511595, AC011472,7, AF271350. 1. | AWYD8374, HF970842, BH933194, ALI 5522, ARG3052, AWKG12437, AWK80626, BF81810, BF808090, ARVI 180937, ADF92090, ARG51420, ART54511, ALIS8856, BF81306, A7R60176, AR059972, BF511821, AALIS88506, BF475287, AAUG1641, AR05792, AALIS446, BF9030, BF857717, AWWS2098, A2L21575, AALIS88506, BF475287, AAUG1012, ALIS9802, AAUG1010, BF8877, ARG51095, AALIS6000, ART60019, ARR90020, AARS706, AASA7578, BF511571, R77685, BF67157, AARS9029, BF9002019, ARIS2065, BF56444, C21055, ALI362311, ARF47395, 1. | AA552985, AA314716, BE778519, BE894256, BE779796, AA228139, AI802948, AC005325. 1. | ALGEZODO, BENDORA, ALSZIGNE BUSTEZORE RESPONSA, DELEACHDO BEILL SUICHOUSDI, BENDORAN ALGESON, BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN BENDORAN | ALS156493, ALS140, ALS767, ILGORORY, BERNOSTS, BEQUSSER, ALS29147, ALS1580, ALS15400, BERNOSTS, BESTZOON BESTGOOLDER, BERNOSTS, BERSZZOON BESTGOOLDER, BERNOSTS, BERSZZOON BESTGOOLDER, BERNOSTS, ANWESTS, BERNOSTS, BESTZOON BESTGOOLDER, AND SEGGES ANY STOCKNISTS, ANY STOCKNISTS, ANY STOCKNISTS, AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND SEGGES AND |
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|                                                                                                                                                               | 15 - 989                                                                                                                                         | 15 - 2286                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 15 - 1240                                                                          | 15 - 997                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 15 - 2383                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| į                                                                                                                                                             | 1 - 975                                                                                                                                          | 1 - 2272                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1 - 1226                                                                           | 1 - 983                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1 - 2369                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| $\vdash$                                                                                                                                                      | 1307726                                                                                                                                          | 699812                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1087335                                                                            | 629552                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 765310                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                               | 135                                                                                                                                              | 136                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 137                                                                                | 138                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 139                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                               | HLQDR48                                                                                                                                          | HLTHR66                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | HLTIP94                                                                            | HLWAA17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HLWBK05                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| AA378783, BF35343, AA600145, AA887867, 146028, H48275, AA360706, AD50801, BF884388, HILIU02, BF864365, AA278108, AR86165, EA5026, RE0165, RE01 | AA923172, AII39607, AIS6739, AI802946, N30680, AI277957, AI277237, BE7315040, BE838082,<br>BF934274, AWY97336, AW797335, BF987948, AW873630, AI806044, AK026806.1, AC003991.1,<br>RA027807, 1. | AWG7977, AAS24980, ADG1840, AWG15257, AA87T458, A135672, AWG7080, N66443, AA528268, A272599, N26777, AA064802, H999086, AA7070372, AZ5944, AA906772, AA104802, H999086, AA7070372, AZ5944, AA906772, AA36903, H999086, AA7070372, AZ5944, AA906772, BA46873, H89408, H99408, AA7070471, BA57870, BA578700, AW999226, BA776458, AB674714, AA596487,17, AK075020, L1, AK076182, H984718, HP878700, AW999226, BC078144, LA596487,17, AK075020, L1 | AV764526. | AA464480, A173816, AW970172, BF34682, BE004609, A1097351, A1051171, AW085704, N30904, A1950173, A1718945, BI6402, BG354604, AN64010, AN401489, W76242, H64144, AWQ14133, AA29655, AW388106, BF751672, AA693868. | AT 701025, IRRSAS, RESORY, ETROPOR, ERGROSCA, EPPA-917, AV10619, EPSSR1, IRFSHIST, BETSHIST, ALISSBOOK, ALISSBOOK, ALISSBOOK, ALISSBOOK, ALISSBOOK, ALISSBOOK, ALISSBOOK, BETSHIST, BETSHIST, ALISSBOOK, ALISSBOOK, AND STAN STAN STAN STAN STAN STAN STAN STAN |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1 - 2067                                                                                                                                                                                       | 1 - 632                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1 - 298   | 1 - 1262                                                                                                                                                                                                        | 1 - 1209                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 609262                                                                                                                                                                                         | 460619                                                                                                                                                                                                                                                                                                                                                                                                                                         | 778075    | 553514                                                                                                                                                                                                          | 638042                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 140                                                                                                                                                                                            | 141                                                                                                                                                                                                                                                                                                                                                                                                                                            | 142       | 44                                                                                                                                                                                                              | 145                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | HLWBY76                                                                                                                                                                                        | HLWCF05                                                                                                                                                                                                                                                                                                                                                                                                                                        | HLYAC95   | HLYAP91                                                                                                                                                                                                         | HLYES38                                                                                                                                                                                                                                                                                                                                                   |

| AA173218, BE968449, BF096068, BF869076, AW893125, H47099, AV730261, AW409222,                                                                                          |
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| AC005106.1, AL135314.1, AC003388.1, AL353143.11, AC004045.1, AL450333.13, AC008962.8, AC005768.17, AP002853.3, AC003466.17, AP000880.4, AL157688.4.                    |
| AL121939.12, AC010369.6, AC004946.1, AL139327.18, AC011198.2, AL135780.11,                                                                                             |
| AK022205.1, AC069304.7, AL109769.4, AL049781.5, AP001669.1, AL355520.8, AL133517.11,                                                                                   |
| AC026398.4, AL353133.7, AL357153.4, AL049796.28, AF002997.2, AL356498.10,                                                                                              |
| AL360020.15, AL121938.6, AP000826.4, AL590964.8, AL022399.2, AL121949.13, AC007065.5,                                                                                  |
| AC0231545, AL008722.16, Z82212.1, AL158965.10, AP0011794, AL360272.23, AC006379.2,                                                                                     |
| AC0342154, AC0205494, AL359973.11, AL357272.10, AL117191.6, AC012499.7, AL163052.4, AC010478.5, AC008488.7, AC004664.1, Z82203.1, AC012492.9, AL353573.10, AC023866.7. |
| AC018659.35, AC007392.3, AL390035.10, AL353811.12, AL121980.14, AP001880.4,                                                                                            |
| AP000629.4, AL357892.13, AL022401.1, AL137191.5, AC003013.1, AL136101.7, AC006399.6,                                                                                   |
| AL355807.11, AL391475.7, AC003953.1, AC026773.4, AC026409.3, AC010289.7, AC002349.1,                                                                                   |
| AL035422.12, AC011359.5, AC018705.10, AL050401.5, AC007250.2, AL022101.1, AL358337.1,                                                                                  |
| AL353788.33, AL008713.1, AC006395.1, AC090645.1, AL358335.4, AL008633.1, AC020977.5,                                                                                   |
| AL121947.14, AC016591.6, AC090497.2, AC083862.2, AL136110.17, AC010969.11,                                                                                             |
| AC006313.1, AL035397.4, AL160236.4, AL389888.8, AL590675.3, AC013242.7, AC024610.6,                                                                                    |
| AC010749.3, AC009404.5, AC007248.3, AC009901.6, AL365179.30, AL158033.18,                                                                                              |
| AL031671.12, AC006061.1, AC007032.2, AC067744.5, AP001972.4, Z78022.1, AL121694.4,                                                                                     |
| AB017651.1, AL109662.3, AL035427.17, AL109845.8, AL079333.7, AL133348.8, AC010209.13,                                                                                  |
| AL359914.14, AL049821.6, AL139396.17, AC019097.5, AL117327.5, AC022413.4, AC004006.1,                                                                                  |
| AL162587.20, AL356789.16, AL022097.1, AC073325.8, AF003529.1, U82696.1, AC007489.3,                                                                                    |
| AC009039.6, AL163281.2, AC069543.4, AF274856.2, AL359012.7, AP001573.3, AC025471.5,                                                                                    |
| Z70233.1, AC004979.1, AC023347.8, AC021133.5, AL590363.6, AL133386.3, AL160471.5,                                                                                      |
| AC020987.8, Z95325.2, AC069298.8, AL157791.4, AC004535.1, AL355540.12, AC009122.8,                                                                                     |
| AC012450.9, AC026445.4, AC008860.6, AC016612.5, AL080316.8, AC002407.1, AC011745.4,                                                                                    |
| AC007376.9, AC005029.1, AK022413.1, AC090004.1, AC069462.2, Z85997.1, AL590043.7,                                                                                      |
| AF128525.2, AC007256.5, AC025040.7, AL078600.15, AL500522.9, AF064865.1, AF235098.1,                                                                                   |
| AC002086.1, AC079316.15, AC034305.6, AC020896.5, AC008886.5, AC008834.6, AP002088.2,                                                                                   |
| AL159970.16, AL157911.4, AC002458.1, AL590034.10, AC073387.4, AC007743.3,                                                                                              |
| AC005510.3, AC005016.1, AC078848.3, AC022710.10, AC022073.13, AL356956.11,                                                                                             |
| AL160052.21, AL137013.4, AC004050.1, AC005272.1, AC005826.1, AL158147.17,                                                                                              |
| AC008173.2, AL034399.6, AL158823.11, Z99570.1, AL121577.1, AC021237.5, AC021001.5,                                                                                     |
| AL138920.11, AC069294.5, AF280107.1, AF117829.1, AL109921.21, AP000457.3, AL033375.2,                                                                                  |
| AC008071.2, Z71187.1, AP002076.3, AL139106.12, AC004083.1, AL357312.8, AL162571.9,                                                                                     |
| AL162373.16, AL133339.13, AL161450.14, AC005187.1, AL356473.11, AL353691.12,                                                                                           |
| AC007000.2, AC018741.3, AC013429.12, AC008265.15, AC044791.6, AC068712.6,                                                                                              |

| AC0016617.5, AC000845.2, AC012152.12, AL445669.9, AL163248.2, AF207955.1, AC004668.1, AF109076.1, AC013562.6, AL139231. 13. | ALS8273, AW139111, AA66589, ALS82741, AL120239, H51572, A1122619, A1124509, BF366373, AR660 1150906, R86835, BF836623, BE884648, AF070673.1, AF030196.1, AL161976.1, BC008337.1, | BEP2550, BET3900, BER9124, BET24745, RE65930, BP91187, BE66948, BE33662, BET47520, BEP2550, AT33012, A492192, BE207602, ANT275412, AA934656, ANT3907, AT1994.09. ANT39644, A158173, BE20764, A176236, ANT5737, A146377, BE64146, AA506161, BP062047, AR192447, AND S22524, A1762361, A7768708, A776379, BE64146, AA506161, AP127501, AP127601, AP127501, A | BEP00239, AII14496, BE047613, AI609021, AI478544, AJB49665, R96283, AI205799, W39248, AI670908, T10976, AAM70919, AI243978, AW854183, A7196472, BE883-077, AW975683, AA654405, AI12888, AA7390911, AA545731, BE222003, AA7390927, C21177, AA721678, AI478489, AL1371399, AL139035, A, AL1371390, AL39035, A | BF026.99, BE277091, A134297, BF027218, BE390121, BE387283, AL514638, BE38858, A1564111, BE389119, A166899, BE391988, ANY306551, AA676232, BE870993, BF002101, BE277034, BE172957, BE276552, BF127490, BF86609, BE386944, AV207225, AA551687, BE17320, BF113131, AA707744, BF033868, AA707747, BF033868, AA707747, BF033868, AA707747, BF033868, BF073886, BF073888, AA707747, BF073886, | ANDTOSIS, ANDTOSIS, ANDSOSIS, ANDSOS |
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|                                                                                                                             | 146                                                                                                                                                                              | 147                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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| A7344041, US2111.2, A70088965, A11216551, AP031112, A7009320,7, A70040871,<br>A1121992,34, A1160410, A11878920, AL0312281, A700667111, A1121752.13,<br>A11570619, A7025418.2, A7007012.1, A70064820, A1354670, A | HERGYAY, BFYAGE BERGYAR, RESPEZIS, RESPEZIS, PRESPEZIS, PROFEZIS, PROFIZES, MAT 1793, W99515, AVE24641, BFYAGEAG, BERSTASH, RESPEZIS, PROFIZES, ALGSGO, BERSTASH, ALGSGO, BERSTASH, ALGSGO, BERSTASH, ALGSGO, BERSTAG, ALGSGO, AND ALGSGO, AND ALGSGO, AND ALGSGO, AND ALGSGO, AND ALGSGO, ALGSGO, BERSTAG, ALGSGO, AND ALGSGO, AND ALGSGO, ALGSGO, ALGSGO, AND ALGSGO, AND ALGSGO, ALGSGO, ALGSGO, AND ALGSGO, AND ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, AND ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, AND ALGSGO, ALGSGO, AND ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALGSGO, ALG | MD29546, AIRSPAT, AASTITI, WIN1913, AASTSAG, AR69870, AAST0899, AAST0942, AAST094, DAGFT29, AAST294, DD0078, AAST0949, AAST0941, AAST094, AAST0946, AAST0949, AAST0946, AAST0949, AAST0946, AAST0466, AAST0466, AAST0466, AAST0466, AAST0466 |
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|                                                                                                                                                                                                                  | 151                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 152                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| ACOB4934, Z8811,7, ACO68297, ACOPTIA,1, ACO16828,3, ACO252813, AL1581914,<br>ACO168084, APO017211, ACO680733, ACO694761, AL1565639, AL06979112, ACO660994,<br>ACO168142, D400711, ACO696711, AL1582814, ACO665311, ACO66570, US33311,<br>ALS1540613, AL15787711, AL14223612, AL1067014, AL1602694, ACO663128,<br>ACO66821, AL15787711, ACI4223612, ACO67711, ACI402694, ACO663128,<br>ACO66821, AL023807, ACO16185, ACO76714, AL166695, ACO60322, AL121862,<br>ACO68631, ACO2646, AL1587878, ACO763863, ACO69122, ACO69523,<br>ACO698231, ACO2646, AL1587878, ACO66803, ACO16227, ACO69523,<br>ACO698231, ACO69646, AL1587878, ACO66803, ACO16227, ACO69523, | T65556, BF952979, F09666, AA995112, AA983746, AA983748, AP001972. 4. | ### 19538198 JE358186, JEF57884, APG-257, AAR41706, AL02906, Deposedor, ALU19409, ALU19409, ALU19506, ALU19506, ALU19506, ALU19506, ALU19506, ALU19506, ALU19506, ALU19506, ARU19509, ARCPORT, ARTHORY SERVING THE STEED GIA STANDARSON, ALU19506, ARVIDSOR, ARV |
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| AMUSSAND, AASSEQ, AVTOSTA, AVTOROSS, BETATZO, AASSTTOB, AASSEST, BETATSO, AASSTTOB, AASSTOP, AASTTOP, AASSTOP, AASTTOP, AASTTOP, AASSTOP, AASTTOP, | BR225687, BIS28463, ALL34549, BR32481, BR9449, AW852129, AW852464, AU08217, AU64149, BR52851, BR528463, ALL34549, BR52872, AVR06444, AVR05212, BF76449, ALL4679, BF82875, AVR06466, AV917341, BF84601, ALL35082, AW001418, AD50923, BF769499, ALL46791, BF828754, AW85010, AV82609, AV8260 |
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| AC0103384, AP0000431, AP0001111, AP0017161, AP0004243, AP0002921, AC0733214,<br>AL1333014, AL138743.5, AL06033812, AL44424213, AC068715.5, AC069003.7,<br>AL480026.10, AC008493.4, AL3533426, AC003300.1. | ALDHRIND, ALSTONIS, BETSTROM, BETSTSS4, BETSTS174, BETSTS174, BETSTS26, ALSTONIS, ALGOROU, BETSTS26, MULTICATO, ALSTONIS, BETSTROM, ALGOROU, BETSTS26, AUGUSTS26, ALGOROUS, ALSTONIS, BETSTS26, AUGUSTS20, ALGOROUS, AND ALGOROUS, ALGOROUS, AND ALGOROUS, ALGOROUS, AND ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, ALGOROUS, A |
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|           |     |        |         |           | AF115392.1, AL389947.1, AF232009.1, AL050155.1, AL050366.1, AB050510.1, AK026464.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|           |     |        |         |           | AF131821.1, AK027144.1, AL137533.1, BC003658.1, AF245044.1, AB052176.1, AL137711.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|           |     |        |         |           | AF274348.1, AF274347.1, AL137480.1, BC002733.1, AL359941.1, AL133637.1, X82434.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|           |     |        |         |           | BC008364.1, AL080146.1, BC004925.1, AB060897.1, BC005168.1, AB056421.1, Z82022.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|           |     |        |         |           | BC003590.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|           |     |        |         |           | AF132730.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|           |     |        |         |           | AL162083.1, AL137271.1, AF218006.1, BC003569.1, AK027204.1, BC004336.1, AL583915.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|           |     |        |         |           | BC006287.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|           |     |        |         |           | AK027096.1, BC001785.1, AK027173.1, BC006410.1, S77771.1, Y14314.1, AL133062.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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|           |     |        |         |           | AL080154.1, AK000636.1, AB055331.1, AF339775.1, AK025435.1, BC008037.1, BC006458.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|           |     |        |         |           | BC003056.1, AL390184.1, BC007571.1, AK025350.1, AL110221.1, AK024747.1, AF262032.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|           |     |        |         |           | AL133084.1, BC002365.1, AK024992.1, BC007206.1, BC000550.1, BC006091.1, AB048913.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|           |     |        |         |           | AY034001.1, AK026532.1, AL162002.1, AF026816.2, BC000199.1, BC008649.1, BC003591.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|           |     |        |         |           | AJ299431.1, Y13350.1, AK025099.1, BC004362.1, BC007460.1, AL512733.1, AB056420.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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|           |     |        |         |           | AL133049.1, AF061573.2, AL157433.1, AL136784.1, BC008417.1, BC005070.1, AK026528.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|           |     |        |         |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|           |     |        |         |           | BC007021.1, Y14040.1, AF218000.1, AF141289.1, AK026613.1, AL117460.1, AF126488.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|           |     |        |         |           | AL080139.1, AK027365.1, AJ296345.1, AL137298.1, AL137716.1, Z35309.1, AL137627.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|           |     |        |         |           | AK000476.1, AK026550.1, AL359624.1, AL389939.1, AB048953.1, AL512684.1, BC000253.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|           |     |        |         |           | BC002370.1, BC002849.1, AF217987. 1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HNFIY77   | 164 | 634551 | 1-1198  | 15 - 1212 | BE778688, AA350580, AW451334, BE247283, BE242191, AI640492, AA078462, BE242141,<br>  AW003105 A 4336368 D54880 A1010100 A1871303 A1367818 BE304188 A1858601 A C000413 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|           |     |        |         |           | AMMOSTOS, AMSTOSOS, AMSTOS |
|           |     |        |         |           | ACU/2032.6, ALU3331/.1, ALI61/4/.3, ACU1869/.4, ACU03663.2, ALI339093.13, ALI33/44.4,   AC008073.3, AC008484.2, ALI33/44.4, AC008073.3, AC008484.2, ALI33043.2, AD000386.1, AC036141.7, AC03668.5, AC03668.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| UNIETEO7  | 165 | 577013 | 09-1    | 719 51    | A A 4 2 70 61 A A 4 2 6 61 5 7 7 2 7 5 0 A C 00 7 10 1 A C 00 4 10 5 0 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 0 7 5 |
| (OJCJNII) | 67  | CIO//C | 700-1   | 010-61    | ACHARIOTE, ACHIGOUS, D. 16.194, ACHOROMIS, ACHOROMIS, ACCORDISS, A |
|           |     |        |         |           | AL109897, 30.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| HNGDJ72   | 166 | 532619 | 1 - 510 | 15 - 524  | AC027689.10.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| MAZ73971, AID5058, MAYS7054, MAS5059, LA ACOMOGNI, AGD ACOMONDII, AGNASON, | AL56029712, AC0630231, AC0221245, AC0063907, AC004836.2, AL156984.20,<br>AC00638514, ALL177314, AP0022033, AC0066561, AC007057.3, AL139233.8, AC005079.6,<br>AL23982417, AP00015414, AP000426.3, AL23922.3, | AUJ47901, AA376128, BESGS64, ACB516197, AC0206236, AL445531.10, AC009412.6,<br>AC005052, AC0798817, AL0904212, AC0160576, AR0223801, AC0040327, AP0005551,<br>AC009789, 21, ASSS117, AL35964327, AC0110057, AC008521,5, AC008535, 6, | AA774312, BE670568, AI298480, BE702731, AI088824, AI149772, AA976633, AI870274, AA010606,<br>AA010607, AW957725, AA010628, T33808, T75431, A135800, AC005300.10, AC006946.20,<br>AF307451, 1. | AJ006345.1, AC006590.1, AC003675.1, AC001228.1,<br>AWWINGSR, AWHU094, AIA4475.2, AWWINGSP, AWWINGTIDS, AVX78849, AWWI1094, AIA41094, BG009139, AA157876, BIG000768, AIA5676, AIA4666, AIA41099, BG10919, BG109193, AA157876, BIG000768, AIA5676, AIA41096, BG109196, AIA410976, BG1090768, AIA57876, AIA57876, BG1090768, AIA57876, AIA57876, AIA57876, AIA57876, AIA57876, BG1090768, AIA57876, 
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| 1 - 1028                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 1 - 522                                                                                                                                                                                                     | 1 - 782                                                                                                                                                                                                                              | 1 - 827                                                                                                                                                                                       | 1 - 2114<br>1 - 734                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 499076                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 553552                                                                                                                                                                                                      | 519120                                                                                                                                                                                                                               | 839224                                                                                                                                                                                        | 1041375                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 167                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 168                                                                                                                                                                                                         | 169                                                                                                                                                                                                                                  | 171                                                                                                                                                                                           | 172                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| HNGEP09                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | HNGFR31                                                                                                                                                                                                     | HNGIJ31                                                                                                                                                                                                                              | HNGND37                                                                                                                                                                                       | HNGOI12<br>HNHEU93                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

| BG059924, AA640305, BF439153, H47461, AA507623, AI921744, AA935827, AW265468, BF589864,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| AA831714, AW020682, AL572680, AA601356, A1791720, A1791408, BE049409, A1114755, AW962971, A1828721. AU158433, BE244547, A1251024, AV730440. AW148821, AW474825, AA631915.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| A1791659, AA595661, AA610644, AW023975, AA657392, AW029626, AA834891, A1884404,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AV743067, AI890283, BF944618, AI609992, AI797998, AW970856, BG223384, BE677164, BE150831,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AW836225, AA658890, BE882869, AI031759, BF913232, AA493245, N55076, AA019793, AA523718,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AI888050, H48017, AW576388, AV763460, AW192930, AI076729, AW021847, BF431825, AA652675, AT08665, A A31667, A A31677, |
| BF65698, AA52763, AIG52366, AI445699, BF849260, AIG54466, AW960129, AI52222, AA411337,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| AI640905, AV729090, AI312267, AI570067, AV728973, AW675677, AI701898, BE676910, BF973510,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| A1889614, BG250794, A1571094, AW239465, BF725844, R92703, BE391183, AW028376, AA578711,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| AL590005, AC055740.17, AC090950.1, AL161757.4, AL391375.11, AL158063.12,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AC022542.4, AP002898.1, AL161779.32, AL109804.41, AL157700.13, AL136123.19,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| AL359397.3, AL359273.11, AC007597.3, AP001781.4, AL121932.19, AL109847.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| ALIUWASZ, ALIOSZIGY, ALSYMOSZ, A ACULTAWY, ALISSWOULD, ALIOSZIGY, A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| ACIDISTURY R ADDITISTAL ALBORAGILL, ALBORAGASILL, ACUDISTOLA, ACUDISTOLAR, ACUDISTO |
| ACOUPTING A COOSTREEL AT 1378183 A COURTE, A A 11624015 ALLEGARY, A DOCUMEN.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| AL035400.13, AP000263.1, AL109758.2, AC002844.7, AL139396.17, AC025165.27,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AP000080.1, AL354696.11, AC008651.7, AL354861.11, AL157915.3, AC010585.6, AC007256.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL513548.8, AC005779.1, AC007912.6, AL360227.17, AC008280.4, AC012150.16,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL109627.18, AC025436.2, AC008498.3, AF205588.1, Z95327.1, AL355305.9, AC068319.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AL136418.4, AL139054.1, AL357075.17, AL022578.1, AP003548.2, AL132778.6, AB026898.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL132709.5, AL121989.12, AC005972.1, AL163301.2, AC002302.1, AL137129.4, AC034191.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC002550.1, AC007097.4, AL139021.6, AC006079.1, AL139095.15, AC011247.10,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL138755.13, AL021808.1, AC073964.3, AL121594.6, AL137782.9, AC016950.8, AL133328.13,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL13128.4, AC022367.34, AL138920.11, AC025207.5, AL357150.7, AC008536.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AC005291.1, AC005754.1, AL049712.12, AL354816.5, AL513342.7, AL990039.10, AC0025990.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| AF111167.2, AB020868.1, AL022069.1, AL355343.18, AL160411.25, AC005036.1, AC018719.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL139389.16, AC005228.1, AC002996.1, AL049835.3, AC090509.1, AC010000.5, AC090005.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL161936.15, AC020558.4, AL583856.6, AP002392.3, AL031643.1, AE000661.1, AC016608.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL162853.17, AL031659.9, AC005079.6, AC009953.4, AL121865.7, AL109854.10, AC002395.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL391601.6, AC073125.5, AL161892.9, AL133373.5, AC019184.3, AC009137.6, Z8483.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| AC002381.1, AC017099.11, AL16245.20, AL136234.12, AC009955.4, Z99716.4, AL117337.25,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL138743.5, AC011005.7, AC004847.3, AC008901.5, AC009961.11, AL135783.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AF229163.1, Z844801, AL12520574, AL0354555.0, AC016447, AJ400879.1, AL590387.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AL136526.14, AC063765.14, AC063546.4, AC016651.1, AC063461.4, AC021129.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| ALIOPZIGI, ALICESTI Z. ALIOZDIGI, ACCIOGRSIA, ACCIOZZII, ALIJIZIGIIZ, ALIORGESI, ALIORGESI, ALIORGESI, ACCIONESI, ACCIONE | AC020552.4. | AC012354.8. | MINGOSS, AAMOLI, AMD TIGGA, LINGSLA, ROBES, BEPTSTR, DA. ACKSONG, AMD HOSPS, AAMOLI, AMD TIGGA, LINGSLA, BEPTSTR, DA. ACKSONG, BETSTR, ACKSONG, ACK |
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| AL354446, AL0132561, AL3538118, AL157444, Z997164, Z88445, AR0017091, AL0131311, AC0064043, AC0079417, AC0090427, AC0074044, AL0223561, AC0185393, AC0087556, AC0086225, AC0099457, AC0099591, AC0079574, AC0079574, AC0079574, AC0079574, AC0079574, AC0079571, AC00600591, AC0099501, AC009591, AL3951064, AR0071711, AC00600283, AC0079874, AC0079670, AC0079 | AC021165, ALI6245.20, AC0046851, AC025189.28, ALI393533, AF139813.1, AC007462.2, AC008946, AC013525, ALS024.119, AC022215.3, AC00456.2, AC00493.7, ALI20893.7, ALICSS44.9, AB00082.1, ALI31899.3, ALIGSS44.9, AB00082.1, ALI3652.2, AC04251.5, ALI3690.22, AC034251.5, ALI3690.22, AC034251.5, ALI3693.2, | APPIGEST, AC00013414, AC0048403, AL199166, AL1991861, AC0072014, AC0013412, AC0072014, | ALISEL433, AD006711, AFB12912, AF29642, Z204441, AC009566, AC0007424, AC009566, AC0007424, AC009566, AC0009514, AC009991, AC009962, AC0095655, AC0014526, AC0004771, AC006736, AC0009514, AC0004321, AC0004371, AC006737, AC0000581, AC0004321, AC0095441, AC0071147, AC1098013, AC0003821, AC0004321, AC006736, AC00016376, AC00016376, AC00016376, AC0006378, AC0060572, AC0006156, AC0067376, AC0067371, AC0067371, AC0067371, AC0067371, AC0067372, AC006772, AC0067371, AC0067371, AC0067372, A | 1-1341 15-1355 | ALORGGE, AUI 1795, EB1990) 25, AVI-24040, AUI 1923, BB60701, ALASSH2, AV699709, AV686853, AV722006, BE393567, BE38259, AA708751, A7722911, BF346320, AV772006, BE393567, BE38259, AV7760497, BF380173, BF986814, AV762300, AV75911, AV776346, AV781644, BF39104, AV725020, BF9910, AV759686, AV786174, BF9910, AV7759685, AV776046, AV776014, AV | AA584482, A7734401, AL042905, AV722075, AV737621, BF666736, AA211734, ANV080062, AA787407, AV761909, AV7972207, AV80890, AV87712, AV8078062, AV80890, AV87712, AV807807, AV80890, AV80890, AV877707, AV80800, AV80 |
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| AU140392, AA284247, AW102811, AA722372, AW008212, AU158859, AA640277, U51704,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| AUI55168, BG258140, AW088689, AUI55048, AA577824, BE387734, BE867712, ALI19123, AVIOTOROD A A 601226, DED68610, A 8415820, A CO08440 8, A CO1151, 7, A CO02202, 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AC027319.5. AC005484.2. AC008972.1. AC010469.7. AL109743.4. AC005077.5. AL035398.19.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC020916.7, AC022211.5, AC002301.1, AC018808.4, AP001711.1, AC008745.6, AC000052.16,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL035587.5, AC008720.6, AC007421.12, AC003101.1, AC034193.4, AC025593.5, AC006511.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AF045555.1, AC007374.6, AL096814.26, AC005081.3, AL445685.17, AJ400877.1, AC004985.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| ACUSTS84, ACU09516.19, ACU08445.8, AL03144/4, ACU06028.3, AL03144/4, ACU06028.8, AL0314/4, ACU06028.8, AL03144/4, ACU06028.8, AL03148/4, ACU06028.8, AL03148/4, ACU06028.8, AL03148/4, ACU06028.8, AL03148/4,  |
| AC011465.4, AC008655.6, AC008616.6, AL135928.6, AL513550.9, AL031295.1, AL030335.32, AT040780.4 AC005065.5, AT300060.14 AC011065.7 AP001717.1 A3073040.1 AC007000.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| U8268.1, AC005840.2, AC006530.4, AF111168.2, AC018809.4, AC002477.1, AC011443.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| AC018751.30, AC008622.5, AC023058.17, L78833.1, AC007956.5, Z85986.1, AC072052.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL137067.7, AC018635.6, AC002059.3, AC004824.3, AC026172.3, AC018506.4, AP000116.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL135927.14, AC007227.3, AL445248.7, AL590763.1, AC005914.1, AP001727.1, AL158207.15,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC010320.9, AP000557.2, AL050318.13, AL139809.16, AC008764.7, AC004882.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC007731.14, AJ312686.1, AC008969.5, AC004965.2, AC005037.2, AC000353.27, AC027130.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC087590.1, AL513008.14, AC005520.2, AC005088.2, AL133244.1, AC008551.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AL109976.23, AC011461.4, AL132639.4, AC005089.2, AC010492.7, AC009244.24,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC006930.1, AC007318.4, AC005098.2, AC005399.19, AC005529.7, AC004859.2, AL031584.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| AC005231.2, AF030453.1, AC010527.5, AL034420.16, AC009247.12, AC010328.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC073657.5, AC006120.1, AL117692.5, AP000512.1, AL161452.19, AC022382.3, AL445435.11,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC005722.1, AC005632.2, AL162426.20, AL138721.16, AL163636, AL049766.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AL137792.11, AL391827.18, AC004815.2, AL135901.23, AC020983.7, AC021036.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AL162724.16, AL590762.1, AC011500.7, AC005736.1, AL022312.7, AP003357.2, AL158830.17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC004089.25, AC006538.1, AP000212.1, AC008760.6, AL450226.1, AL163249.2, AC009002.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL121658.2, AF200465.1, AC025438.5, AC091118.2, AC008736.6, AL121601.13, AC004583.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC019205.4, AC010326, AC007676.19, AC018638.5, AC008755, AF001549.1, AC003109.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| AL555480.22, ACU05015.2, AL0/535.29, ACU02295.1, AL035086.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| AL35/515.26, AF168/8/11, AC0/42/0.25, 295152.1, AC0024/0.17, AP001752.1, AC0050/0.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC005332.1, AC005619.1, AC010488.5, AF196779.1, AC006285.11, AC010463.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AC004813.2, AC024561.4, AC007097.4, AC005280.3, AL096701.14, AC002985.1, AC007057.3, AL034370.8, AC007057.3, AD001775.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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1979                                                                                                                                             | 1181 - 51                                                                                                                        | 15 - 1118                                                                                                                                                                                                                                             | 15 - 830    | 15 - 1939                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| AA862707, N95587, AA401399, AA399957, AW511080, AL157879.7, AL021368.1, AL009030.15, AL049987.1, AL133255.13, AL390738. 4. | AI671275, Z69713, 2. AI 528504 AII 51718 AI820674 T04707 A 12247 I V 13241 I AC070145 3 A 1001047 1 | WIGGHDO, AUTSTAT, AUFSTAT, NATSBORY, AUTST IGEA, AUTSTAT, BEBERGER, BIRDTTATA, WIGGHDO, AUTSTAT, AUTSTATS, AUSSBORY, AUTSTATA, AUTSTAT, AUTSTATS, BEGORGES, AUGUSTAT, AUTSTAT, | BE465874, BE465890, AW418562, AW814995, AA721114, AC002543. 1. | ALC21333 BP96664, BIOJUDY, BERG1348, REG980, BR66669, BR67616, IR BER318, RE66019, BRE6112, AW6644, BUG1092, BERG112, AW66430, BERG123, AW66430, BERG320, BE |
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| <ul> <li>W. WOSSES, A. WORGES, B. A. VIDYD933, A. WORGHO, A. VIDSOB, A. W. VIDSOB, A. WORDS, B. A. VIDDOB, A. WORDS, B. A. VIDDOB, A. WORDS, A. WORDS, B. A. VIDSOB, A. WORDS, A. WORDS, B. A. VIDSOB, A. VIDSOB, A. WORDS, B. A. VIDSOB, A. VIDSOB, A. WORDS, B. A. VIDSOB, A. VIDSOB, A. WORDS, B. A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB, A. VIDSOB,</li></ul> | ARIN (GOZ) BEF4419 BCHOSAC, 21 GITL BASA, ALION BERNAGON AWS5413, WIDTL2, AAJ 33346, BEBLATDY, AZUMCO, AWI (GODA, AND STEER) BERNAGON, AZUMCO, AWI (GODA, AND STEER) ALISOSON, AND STEER, ALISOSON, AZUMCO, AWI (GODA, ALISON) BRINGH, AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND STEER AND S |
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| 141144, AAD2018, AWG0454, T4030, BE936681, BE170970, AA02297, BE1907066, AWAT0024, AA706779, AV721515, AW804544, AA776685, AI191274, WW64441, T41173, BE930067, AL22457, BEBS30616, WW85525, AW804644, AL1045003, AW804520, AL1040303, AW805180, AURS26520, AWSW39454, AW804984, AURS26520, AU | ACOUSTON, ACCOMPATA, ALTITATAZA, ACOUDORAL, ACOUSTA, ACCOMPATA, ACOUSTA, ALTITATAZA, ACOUDORAL, ACOUSTA, ALTITATAZA, ACOUSTA, ALTITATAZA, ACOUSTA, ALTOROSTA, ALTOROSTA, ALTOROSTA, ALTOROSTA, ACOUSTA, A | Albesqua, Albasoyl, Awizintza, Aifsoza, Narles, Nafors, Ail 88511, Abitososi 14, Angosyl, Awastoria, Anderdon, Arkosta, Albasosi, Arantolia, Liszorsa, Androia, Allostos, Albestos, Albestos, Androia, Albestos, Androia, Albestos, Albestos, Albestos, Androia, Albestos, Albestos, Albestos, Androia, Albestos, Albestos, Albestos, Androia, Albestos, A | AGROPRE, BEPOGRAP, AVTGSNE, BEBERTFJA, AVROBIGE, AVROTISAS, ALUGHGON, ALLOGON, ALLOGON, ALLOGON, ALLOGON, ALLOGON, ALLOGON, ARCHIVER, ALLOGARI, ERGOTS, BEFTSSI, BELGGON, ALLOGON, BESUTSSI, AVASONG, AWGSTI, BEGGON, AWGSTI, BELGGON, AWGSTI, BERGGON, AWGSTI, AWGSTI, AWGSTIG, AWGSTI, AWGSTI, AWGSTIG, AWGSTI, AWGS |
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| ALLIBORDI P. ALLISWES, ALGORISTI, A. (1919)00.5, ALSISGS4,10, ALLISWES, ALGORISTI, A. (1947)15, A. (1947)15, A. (1947)15, A. (1947)15, A. (1947)13, A. (1947)14, | AP001206.3, AP001329. 3. | AUJ40137, AW27142, BFS11622, AWS90034, AW997845, AW997846, BED6651, AW997843, AW597843, AW57047, AW4404021, AW45119, BE047152, BF946570, BF946580, BF946580, AW997843, AW57906, BF912501, ZV075716, BF047152, BF049620, BF944755, AN325530, AW962066, BF1244, AW129784, BW272716, BF049402, BF049400, BF24475, AN325530, AW997644, AN315452, BF049675, BF049676, BF979676, AW37044, AN315452, BF049670, AW37044, AN315452, BF049670, AW37045, AW37045, AW37052, AW37049, AW37045, AW370 |
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| Table 4.007918. ALISPYTE-PET-246. AVEGIST 1 PEP-64633. PEP-64633. PEP-64634. ALISPATE ALISPYTE ALISPATE AVEGIST 1 PEP-64633. PEP-64633. PEP-64634. ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALISPATE ALI | BROLI 1560, R0072554, ALSSS10, BROSRAP, BRETACKAST, BRETACH, ASSSTT, BGIGSS40, ACADSTS10, BROSRAP, ALSSSTS10, BROSRAP, ALSSSTS10, BROSRAP, ALVISTAT, ARROTASA, AVROTSA, AVROTSA, AVROTSA, AVROTSA, AVROTSA, AVROTSA, BROSRAP, ARGARIA, ARGARI |
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| AMG6994, BES0012, BES9911, AND 141191 HARDZ, PRR60597, BES214, AND 170, AUSSETS, AAMG6491, ALSOURGZ, AASBOSG, AARDISK, BER01214, BEJ07909, A083746, AASSETS, AASBOSG, AATSTAQ, ABOSGZZ, AAGSTSK, BES0219, ERGK, AARSTSTS, BESSSST, ALKSOSD, ALSSES, AATSTAG, ARDSTS, AWGSTOM, AWGSTOT, ANS90204, ABS1485, AWSTSON, AASSONG, AAAGSTG, AAUTONG REGT238, BET09947, AAAG441, BESGSS, AABSTS, AAASSONG, AAAGSTG, AMBSSSZ, ALADYD, BESTSTOM, BESSTOM, BESDSSS, AAATSTS, AAAGSTG, AABSTS, AAASSONG, ABSTS, AAAGSTG, AAATSTSON, AAAAGSTG, AAABSTS, AAASSONG, BESSTONG, AAAAGSTG, AAAGSTG, AAATSTSON, AAABSTS, AAAAGSTG, AAATSTSON, AAAAGSTSONG, AAAATSTSON, AAAAGSTG, AAABSTSONG, BESSTONG, AAAAAGSTSONG, AAAATSTSON, AAAAGSTSONG, AAAATSTSON, AAAAGSTSONG, AAAATSTSON, AAAAAGSTSONG, AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA | AII47736, F-24079, AID91459, AI732547, AXD91242, AU112459, BF930840, BF308519, AI659402, AA719317, AA602231, AI752815, AW967109, AV694013, AA7049486, AI218622, AA646454, AR0218411, AC0067771, AL0314318, AC0074061, AC0023011.14, AC0041431, AC0164311, AC074121.16, AC00675401, AC00559297, AL35470617, AC00551667, AC0167403, AC0167408, AC016740 | ALE 19765, ALE 1976, BIRDORG, BERGRAGA, BELTAPAT, BEISTSHE, BEPSTOSA, BESSORO, BEPSTATZ, BELESTSHE, ALE 1976, ALE 1976, BERGRAGE, BETATUR, BESCHOL, BERGRAGE, BETATUR, BESCHOL, BERGRAGE, AND SERVEN, BERGRAGE, BETATUR, BETATOR, BERGRAGE, AND SERVEN BETATOR, BETATOR, BETATOR, BETATOR, BETATOR, BETATOR, AND SERVEN BETATOR, BETATOR, BETATOR, ALISTSKI, ALGORIA, BETATOR, BETATOR, ALISTSKI, ALGORIA, BETATOR, ALISTSKI, ALGORIA, BETATOR, ALGORIA, BETATOR, BETATOR, ALGORIA, BETATOR, ALGORIA, BETATOR, BETATOR, ALGORIA, BETATOR, ALGORIA, BETATOR, BETATOR, ALGORIA, ALG |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1 - 1237                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 - 1525                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 882176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 871221                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|           | _          | -                  |           | AAS70075, AL039562, AA827726, AW246353, W04715, H89133, BF125722, AA626654, AW246566, AW519242, AI689744, AI752669, AW247535, AA077415, AW129363, AI202252, AA628809,     |
|-----------|------------|--------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           |            |                    |           | BE869982, AI208476, BE206952, AW511835, AA037397, BF828156, BG031018, BE513491,                                                                                           |
|           |            |                    |           | DE JOSUL, AW 149144, ALI 89/26, AAU 78621, BE21.59/5, BF 194/52, 114/888, AW 924928, AA8U64U4,<br>AWO80710 BF847605 AA077110 AA319080 AA101354 AT214676 AA434187 AA932091 |
|           |            |                    |           | BF837875, BE140453, AA428843, R11194, AA778244, AA077601, AW082443, N90686, AI675644,                                                                                     |
|           |            |                    |           | BF794477, W05073, A1520907, AL046053, AW298462, AA496322, T50535, BC008084.1,                                                                                             |
|           |            |                    |           | AK001129.1, AK021688.1, BC007488.1, AL117883.1, AC006014.2, AB014518.1, AC005488.2,                                                                                       |
|           | _          |                    |           | Y16/041, N34250, N81046, AA036807, AA135346, AA236044, AA262692, AA938381, AA204918,<br>AA402082, AA455506, AA455507, AI217271.                                           |
| HRACJ35 2 | 203 877    | 877666 1 - 2063    | 15 - 2077 | BE906771, BE218907, Al912661, BE670671, BG166321, AW167740, Al698131, Al796048, BF476110,                                                                                 |
|           |            |                    |           | AW952474, AW474992, AW149683, AI814137, BE436724, AA452391, AI635719, AI422285,                                                                                           |
|           |            |                    |           | AI675301, AW301634, AI800309, AI023300, AI269915, AA054467, BF062213, AI220479, AA991181,                                                                                 |
|           |            |                    |           | Al159765, W88683, Al623293, Al205308, AA043330, AA461136, BE669608, Al032982, AA634903,                                                                                   |
|           |            |                    |           | AI361429, AA877688, BF681677, AW868366, AI683625, AI094869, AI268543, AI040482, AA460833,                                                                                 |
|           |            |                    |           | AI042583, AI800329, H40189, AA041196, AI420048, AA127006, AI023081, AA045134, T96696,                                                                                     |
|           |            |                    |           | M79132, W23483, BF000996, AI161385, BF476853, AI521085, AI984382, AA492294, AA016124,                                                                                     |
|           |            |                    |           | N95081, R13864, AI146307, W28330, AI022619, T19296, AA410735, BF573582, BF056915, T30952,                                                                                 |
|           |            |                    |           | AI971069, AA043329, AA126627, AA215786, R07660, BE833878, BE833866, AA329616, BE833882,                                                                                   |
|           |            |                    |           | BE833868, AA977851, Z41866, AA226105, AA126801, AA056673, AV693019, AA216384, R18560,                                                                                     |
|           |            |                    |           | AA041433, AW244035, R05716, AA868767, BF222351, H40140, AW589719, AV686312, BF207973,                                                                                     |
|           |            |                    |           | AA226035, AA228673, AI817777, AI420271, AV747189, AI248289, R05717, T30818, BF847400,                                                                                     |
|           |            |                    |           | Z38161, AA879250, D57208, R37006, AA319785, AI699205, T96591, AW945698, AA225132,                                                                                         |
|           |            |                    |           | AA333327, AA045610, D57177, AA226695, AA045355, BE905736, BE670421, AW469919, BF000980,                                                                                   |
|           |            |                    |           | AW771589, BF871391, F19153, AW152062, AW964837, R41427, BE242459, BF445505, AW373047,                                                                                     |
|           |            |                    |           | AW069103, W88670, AA761464, BF844537, AF107834.1, AF119386.1, AP003117.2, AF107833.1,                                                                                     |
| $\dashv$  | -          | 7                  |           | AP003111.1, AP003112.1, AP003477. 2.                                                                                                                                      |
| HRGBL78 2 | 204 910133 | 133   1 - 2094     | 15 - 2108 | BE271199, AW575245, BF794609, BF797900, BE559773, BE384088, BE513826, BE270971, BF572042,                                                                                 |
|           |            |                    |           | BES60978, BF690655, BE674800, BE275832, BF303959, AW205367, AW402801, BF203242,                                                                                           |
|           |            |                    |           | AW402242, AW402928, BF305905, BE466652, BE892536, AW403946, N24246, AW968460, AI654541,                                                                                   |
|           |            |                    |           | N28316, BF572179, N29315, N38941, AW383418, AA458944, AI276242, BE729612, AA215300,                                                                                       |
|           |            |                    |           | N33010, AW383426, AW383396, N20230, BF692515, AI439520, N29316, AA459158, N25452,                                                                                         |
|           |            |                    |           | W03476, AW383428, AW402824, N30453, N28949, N21241, AI760983, N20533, AI434284, BG025865,                                                                                 |
|           |            |                    |           | N72999, N20563, BF896859, AW403434, N67502, AI470743, N73074, AA837208, AW407871, H84381,                                                                                 |
|           |            |                    |           | AW404443, N26470, W02963, AI864746, N46511, W02298, H98912, H84382, N35519, H99497,                                                                                       |
| +         | -          | -+                 |           | BF890914, AA761778, N71796, AI222330, BC006521.1, AL359541. 11.                                                                                                           |
| HROAJ39 2 | 205   1181 | 1181699   1 - 1132 | 15-1146   | T66247, BE081925, R34513, F12057, AA852760, AA125904, BF996914, BF107281, BF743278,                                                                                       |

| BF742834, AB040901. 1. | MORDI III, AWILOSG, CIT730, AWIZ1912, AUSSAN, AUISTAN, AWISTAN, AWISTING, AMIDSHA, AURSTAN, AMIDSHA, AURSTAN, AMIDSHA, AURSTAN, AMIDSHA, AMIDSHA, AMISTON, AWISTON, AMIDSHA, AMIDSHA, AMISTON, A |
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|                        | 8661 - 51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                        | 1 - 1984                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                        | 827306                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| ARIDISTS4, ACROSS22, ACROSSES, ACRIFFIS, ALSSES, ACROSS21, ACROSS22, ACROSS22, ACROSS23, ACROSS2 | AI770009, BE467511, AWS93206, AA434584, AI767843, AA780308, AA563708, AA317400,<br>AA433906, AB021123.1, AC005598,6, AF361936, 1. | A WWGASIS, BI-RGRONG, BI-22004, AURSEGS, BI-BANGFONG, BIRLD-BQ-A, ALIZSEGT, AAASSSSAQ, AAWARGES, ALI ISROIL, 244033. BI-9204855, ZAGOOI, 1872.0, R9990, ILII-649, RS8-21, E07708, RS5771, R85396, FUGSS, R41971, AABSGS13, TIRSROI, AWOSI 331, FUGSS77, Z40771, AAISSGS1, R878, ARIVER, 
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| HSDJM31 211 | 491112  | 1 - 547 | 195-51   | AW07217, 1875394, ALISTRON, ALISTRON, ALISTRON, AROUSTS, |
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| HSDSB09 212 | 1301498 | 1 - 795 | 15 - 809 | BF42333, AI8618S1, AD40993, AJ795956, A107484, A1640759, AW006868, AW241621, BF592070,<br>AW271387, AW614840, AW450466, AW243423, AIZ44694, A1640517, BF431451, BF431530,<br>A1439169, A1613108, A109388, A1084706, A1245323, AW360335, AA031466, AW235483,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| HSHAX21 2                               | 213 | 612823 | 1 - 1972 | 9861 - 51 | AC005722, 1,<br>BE379784, AL52216, AL520172, BF439334, AI652855, AI766309, BF512139, AI635715, AW299533,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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|                                         |     |        |          |           | AW299897, AI129966, AW411210, ANG-24534, AN92109, AN03484, AN804159, BF184613, AA279212, AR060983, AN80637, AN80637, AN80636, AW151685, AW151668, AW151668, AW151668, AW151668, AW151668, AW151668, AW151668, AW151668, AW151658, AW151658, AW151658, AW1516580, AW1616587, AW151618, AW16118, AW151618, AW16118, AW1618, |
| 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 | 214 | 589447 | 1 - 1289 | 15 - 1303 | HIZTSGN, HIZTSGN, HIZTSGN, AND STATES, AND STATES, AND WASSEGG, AND STATES, AND STATES, AND STATES AND STATES AND STATES AND STATES AND AND AND AND AND AND AND AND AND AND                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| ALIBROSE, SOSILI, ALISROTI, ACORSABA, Y10964, ACORSSOS, AEDROGASCI, ALISTOSIC, ACORSABA, ACORSAB | BEST5623, AL52051, 3 IRS809141, AW239200, BEST4646, BE254556, AV723508, BF055054, AAA23242, AA853047, BESS524, BEIESS24, BESS264, BESS264, BESS264, BESS264, BESS264, BFSS276, BF72971, AW068453, AW176526, AL520612, BF772807, BF809972, AF18433. 1. | HE138R64 RG75347 RE17288, BERD14585, WARSTST AWITSTS BERD1758 RG107205.  RG117084 RE191589, BERJ1504, WOTSTA, AM60736, AWIT9138, BERJ1504, MERD10205.  AA576697, BEPJ1589, BERJ1504, WOTSTA, AA600736, AWIT9138, BERJ13814, AM600486, AT197128, BERJ15039, BEHJ1504, WOTSTA, AA600736, AWIT9105, AM60200, AM17125, BERJ1504, AA41762, AM71016, BET37613, AM62140, AM60140, AM60300, AM71013, AM17104, AM725841, AWIT916, AM18235, AM18040, AW00418, AM60424, BERS101, AM28317, AM416767, AM725841, AW19614, AM18235, AM1909, AM400240, AM60301, AW19764, AM60210, AM19710, BEP30411, TSP56, BEP30411, AM18235, AM19049, AM410290, AM50140, AM50140, AM50140, AM1975, AM1975, AM1976, AM60140, AM1976, AM19776, AM1976, AM19776, |
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| MWIS7548, AWIS7548, AWIS7540, AWIS1012, AWIS1012, AWIS1012, AWIS7548, AWIS7541, F1228, BETT7928, AWIS7540, AWIS7640, AWIS1012, AWIS7640, AWIS7650, AWIS7640, AWISWA, A | BIGHORI, BEYSTON, BESAPEN, BESSERS, BESTSON, AND STON, AND S | NY   71539, AVP090, BGT/B444, WYB00989, ANDROSS, AD27853, AD79643, AAL1489, BFF000, BGT/B444, WYB00980, AAC6969, SAZ7858, AD79643, AAL1488, BFF000, AAC6962, AW90674, BFF0000, AT10958, AAC69649, AT166613, AAL14889, AAR04020, AT101050, AAC69720, AAC6990, AAC69720, AAC |
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| DS709, PEIS-98886, NB7697, TR4473, AA422985, Z19443, AJ918446, AV651701, F00129, AV651262, BE841215, D56990, A15151209, BE813989, AW3649458, AA743770, ALG47888, ALG47889, AW997000, BE840712, AW826774, AW965201, AW359489, AC005350, L | MANYTOTA, AWROTIGA, CARROTTA, ARROPTA, ARROPTA, ANSTOTA, AND SURRORA, AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA AND ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARROPTA ARRO |
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| 0<br>B<br>B                                                                                                                                                                                                                              | 15. 86. 1<br>19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                                                                                                          | 1 - 847                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                                                                                                                                                          | 467397                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                          | 219                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| ·                                                                                                                                                                                                                                        | HSNAD72                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| L441401, AL13630514, AC0106054, AL022323.7, AC004825.2, AC013436.5, AL13872.5,<br>AL359024, AL359024, AC01878.2, AC01150.7, AC0046501, AC007597.3,<br>AL35360210, AL1360394, AC008231.5, AL3907384, AC020931.5, | BE465277, BF593260, AI765036, BE181153, BE181155, AA834498, BF365438. | AC006159,3, AF125348,1, AC084730, 2. | AI991103, AI765351, AA703513, BF939824, AI925701, AW295389, AW976578, AI199421, AI422698, | AI934983, BE501421, AI127932, AA703493, AW297092, AA677025, AA848037, AA814098, | AW404152, AW904298, AW182186, AW197850, AA741121, AA651794, AI678148, AA906044, | F18680, AA743764, AI632270, AW590435, BE045258, AA608892. | AW839808, AA077633, BF919965, AC008171.3, AF041056.1, AC004089.25, AC005081.3, | AC002013.2, AD000029. 2.<br>AV760760, AW968156, AA737309, BE888245, AA640430, AA167792. AL163279.2. AC019205.4. | AC027319.5. AC011811.42. AL449363.12. AC011445.6. AC020916.7. AC003663.1. | AL162615.13, AL121886.22, AC005412.6, AL096840.25, AC007404.4, AL035704.9, | AP001717.1, AC005098.2, AL356915.19, AC003029.2, AE000658.1, AC007739.2, AC010359.5, | AC004867.5, AL022476.2, AC083884.6, AC005512.1, AC009079.4, AC004965.2, AC005932.1, | AL031670.6, AC022217.5, AP002852.3, AC010605.4, AP001725.1, AC011489.6, AC008736.6, | AC005519.3, AC009123.6, ALS90762.1, AC004983.2, AL049776.3, AL138756.23, | AC004166.12, AC008744.6, AC008474.7, AC005011.2, AC008812.7, AC011005.7, | AL034420.16, AL137792.11, AC074121.16, AC016643.6, AL355392.7, AL121594.6, | AC005089.2, AC020913.6, AL022721.1, AL449305.4, AL109827.8, AC006023.2, AC018720.5, | AL035685.21, AL021155.1, AC010102.3, AC007731.14, AC079468.3, AL008730.1, AP001724.1, | AC005666.1, AL391803.14, AC005736.1, AC020908.6, U91323.1, AL121845.20, AC005000.2, | AC008745.6, AC008537.5, AL031005.1, AC026464, AL031727.42, AC011446.6, AC027644.9, | AC0085555, AC004821.3, AL031311.1, AF001548.1, AC009220.10, AC005280.3, AC016637.6, | AP001716.1, AC011491.5, AC004491.1, AL022328.21, AC090947.1, AL135749.3, AC006141.2, | AL354760.11, AL035659.22, AC027126.4, AC005102.1, AC020663.1, AL022323.7, | AL050318.13, AL022322.1, AC008379.6, AC009155.3, AC011485.6, AC016644.7, AC008895.7, | AC000353.27, AC005484.2, AC005274.1, AF053356.1, AL135927.14, AC007227.3, | AC005500.2, AC008521.5, AC009144.5, AC007318.4, AC005288.1, AL161670.4, AC011461.4, | AL133367.4, AC010320.9, AL022315.1, AC005800.1, AC002418.1, AC006101.3, AL391259.15, | Z93023.1, AC006014.2, AC002350.1, AC009570.13, AD000092.1, AC007003.4, AC009131.6, | AC018828.3, AC004929.2, AL138724.12, AL079342.17, Z99716.4, AC002425.1, AL121992.24, | AL096791.12, AL049874.3, AL049759.10, AC005527.3, AC004883.2, AC018711.4, | AL118520.26, AL121653.2, AC025593.5, AC006452.4, AL050335.32, AL139317.5, | AL117348.25, AC006441.13, AL390252.9, AC019206.4, AC007151.2, AC010530.7, Y14768.1, | AP000113.1, AP001709.1, Z93015.9, AC000003.1, Z84466.1, AC006329.5, AC004841.2, |
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|                                                                                                                                                                                                                 | 15 - 477                                                              | 15 - 1930                            | 15 - 1021                                                                                 | 7                                                                               | 7                                                                               |                                                           | 15 - 727                                                                       | 15-1256                                                                                                         |                                                                           | _                                                                          |                                                                                      | _                                                                                   | 7                                                                                   |                                                                          | 7                                                                        | 7                                                                          | 7                                                                                   | 7                                                                                     |                                                                                     | 7                                                                                  | 7                                                                                   | -                                                                                    |                                                                           | 7                                                                                    |                                                                           | _                                                                                   | _                                                                                    | -                                                                                  | 7                                                                                    |                                                                           | _                                                                         |                                                                                     | _                                                                               |
|                                                                                                                                                                                                                 | 1 - 463                                                               | 1-1916                               | 1 - 1007                                                                                  |                                                                                 |                                                                                 |                                                           | 1 - 713                                                                        | 1 - 1242                                                                                                        |                                                                           |                                                                            |                                                                                      |                                                                                     |                                                                                     |                                                                          |                                                                          |                                                                            |                                                                                     |                                                                                       |                                                                                     |                                                                                    |                                                                                     |                                                                                      |                                                                           |                                                                                      |                                                                           |                                                                                     |                                                                                      |                                                                                    |                                                                                      |                                                                           |                                                                           |                                                                                     |                                                                                 |
|                                                                                                                                                                                                                 | 460537                                                                | 892171                               | 413246                                                                                    |                                                                                 |                                                                                 |                                                           | 296868                                                                         | 886200                                                                                                          |                                                                           |                                                                            |                                                                                      |                                                                                     |                                                                                     |                                                                          |                                                                          |                                                                            |                                                                                     |                                                                                       |                                                                                     |                                                                                    |                                                                                     |                                                                                      |                                                                           |                                                                                      |                                                                           |                                                                                     |                                                                                      |                                                                                    |                                                                                      |                                                                           |                                                                           |                                                                                     |                                                                                 |
|                                                                                                                                                                                                                 | 221                                                                   | 222                                  | 223                                                                                       |                                                                                 |                                                                                 |                                                           | 224                                                                            | 225                                                                                                             |                                                                           |                                                                            |                                                                                      |                                                                                     |                                                                                     |                                                                          |                                                                          |                                                                            |                                                                                     |                                                                                       |                                                                                     |                                                                                    |                                                                                     |                                                                                      |                                                                           |                                                                                      |                                                                           |                                                                                     |                                                                                      |                                                                                    |                                                                                      |                                                                           |                                                                           |                                                                                     |                                                                                 |
|                                                                                                                                                                                                                 | HSQFP66                                                               | HSRFZ57                              | HSUBW09                                                                                   |                                                                                 |                                                                                 |                                                           | HSVBU91                                                                        | HSXGI47                                                                                                         |                                                                           |                                                                            |                                                                                      |                                                                                     |                                                                                     |                                                                          |                                                                          |                                                                            |                                                                                     |                                                                                       |                                                                                     |                                                                                    |                                                                                     |                                                                                      |                                                                           |                                                                                      |                                                                           |                                                                                     |                                                                                      |                                                                                    |                                                                                      |                                                                           |                                                                           |                                                                                     |                                                                                 |

| AC006321, AC016638, AC006545, AC002561, Z38945, AL5107515, AC0073746, AC006321, AL364816, AC006454, AC0060712, AC004126, AL13911321, AC0013710, AC01137410, AC007374, AC00137410, AC007374, AC0073740, AC01137410, AC007374, AC006738, AC006078, AC006370, AC116340, AC006372, AC007474, AC0060865, AC007474, AC00 | ANYTOTAGE HETASBEY, ACTYOROBAL ACTYORAGE HETASBEY, AVATGAGE HETASBEY, ACTYORAGE ACTORAGE, ALB STANDAGE HETASBEY, ACTORAGE ACTORAGE, ALB STANDAGE ACTORAGE, ALB STANDAGE ACTORAGE, ALB STANDAGE ACTORAGE, ACTORAGE ACTORAGE, ACTORAGE ACTORAGE, ACTORAGE ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE, ACTORAGE |
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|         |     |                  |          |           | U238611, AF0009011, AF000001, AF0009341, AL1574311, AL136921, AL420821, AL1407211, BC0083631, AL167211, BC0083631, AL167211, BC0083631, AL167211, BC0083631, AL167211, BC0083631, AL167211, BC0083631, AL167211, AL1590101, AL1590121, AL1590131, AL159011, AL15   |
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| HSYBG37 | 227 | 1056317 1 - 1224 | 1 - 1224 | 15 - 1238 | AL12008.1, AI889193. MINENSAS, BROGAS, BRESSAG2, BERS7446, BET32588, BE527968, BERS86983, BG033426, ARVISSAS, ARVISGAS, RP915018, AVG09944, AIL40709, AW068552, AIRSIRIO, AIR70885, ARVISSAS, ARVISS |

| MR197230, AIPO 965, AUI S6607, BE349416, ANY29033, AU364435, AA897436, BE13.4877, AIZ21593, AIR19272, AIR66430, BEIRSSR64, HESS2014, LASS2019.1, AK0023603.1. AK1527295, A772566, AIR21460, AL522796, AII 99779, AA4406589, AA912764, AW022783. ANY292786, AIR12377, BE128057, AW022564, AP010279, BE446662, BERS7616, AR6246, BERS6203, AM020586, AV017555, AW072456, AW072616, BERS6203, AR06088, AIR1806, AW072617, AW072614, BERS6203, AW072616, AW072616, BERS6203, BEP91146, AII 401193, AA897614, AAA10145, BERS6600, AAA10145, BERS6600, AW072618, BES9204, BES9204, AW086214, AV076409, AAA10145, BERS6607, AR07115, AW270124, BES93291, AW08621, AV076409, AW07251, AV076091, AV076091, AV076091, AV0760871, AV076081, A | AW072387, R83559, AI924465, AI364031, AW513660, BF361111, AA705541, AL162032. 1.<br>BF059486, AW293425, AI190540, AI201131, AI026778, AI016787, AA604883, AW172655, AA393061, | AMUNDAY, A. MUGUSAB, A. MYHAS7, AL48735, AWU1380, AA453589, AIG84921, AMUNDAY, A. MUGUSAB, AL73060, BERUSAB, AA72143, BEG6557, BEITOTIS, AA442130, WU1308, HT72R1, AL51902, AA121906, AA460946, AA721431, BEG6557, BEITOTIS, AA442130, WU1308, HT72R1, A138210, BESH BELL AA92120, AA442130, WU1308, HT72R1, A138210, BESH BELL AB6730, AA721343, BETOTIS, AA440421, BESH BERTON, AA721345, AA147171, BEST BENDAYS, AA14111, AURSZ-SA, RAWGAG, AA771347, BESH BELTON, AA771304, BESH BENDAYS, AA771304, AA15164, AA16164, AA16464, A |
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| 15 - 1022                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 15 - 1028<br>15 - 450                                                                                                                                                         | 15 - 808                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 1 - 1008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 - 1014                                                                                                                                                                      | 1 - 794                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 206980                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 543396<br>381995                                                                                                                                                              | 836072                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 232                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 233                                                                                                                                                                           | 236                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| HTEEB42                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HTEFU65<br>HTEGA76                                                                                                                                                            | нтыри                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

| A1954293, AL120254, AW163464, BG112644, AW021662, A1571000, BG165979, A1927256, A1250852, AV682289 BF812963, A1356575, A1040241, AV682300, A1799364, A1445620, A1040449, A1656270 |
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| BF337602, BE965724, BF814412, BG260037, AA806719, AW264895, BE964614, BF904180,                                                                                                   |
| BF032768, AW151132, BE965432, A1474646, AW089664, A1653769, AW089275, AW020095,                                                                                                   |
| AI434656, Z99428, AW834325, AI923833, AI285419, BGI22101, AC000077.2, AK026885.1,                                                                                                 |
| BC008365.1, AK024570.1, AB063093.1, Y14040.1, X82434.1, AL136748.1, AF078844.1,                                                                                                   |
| AF073483.1, AF285836.1, AL050092.1, AK025958.1, AK025414.1, AK025435.1, AL122118.1,                                                                                               |
| BC003591.1, AF21806.1, AK026613.1, AF218023.1, BC007522.1, BC003410.1, BC007534.1,                                                                                                |
| AF090901.1, AL13632.1, AL13682.1, AK026583.1, BC004310.1, AB0622978.1, AK025407.1,                                                                                                |
| AL389935.1, AL136884.1, AL512719.1, AL359596.1, AB056420.1, AF090903.1, AK026556.1,                                                                                               |
| Z82022.1, AL110280.1, D83032.1, AB055805.1, AL137283.1, AB060826.1, AF262032.1,                                                                                                   |
| AL133049.1, AK026608.1, BC001328.1, AK027164.1, AL049283.1, AL122050.1, AK026522.1,                                                                                               |
| AL137533.1, AL136864.1, S76508.1, AK024545.1, BC008785.1, BC002750.1, BC005890.1,                                                                                                 |
| AK0249441, AL133665.1, AK025099.1, AF155827.1, BC008455.1, BC003120.1, BC003573.1,                                                                                                |
| AL162008.1, BC001785.1, AK025906.1, BC006164.1, AF225424.1, AK025209.1, AK026762.1,                                                                                               |
| BC001964.1, AL122100.1, AB056372.1, Y14314.1, AK026038.1, AK026534.1, AL133081.1,                                                                                                 |
| BC000316.1, AK026630.1, AK025410.1, AF252872.1, BC003122.1, BC005070.1, AL137479.1,                                                                                               |
| BC006807.1, AL162002.1, AL080074.1, AK026784.1, AK027160.1, AB05303.1, AB060887.1,                                                                                                |
| AK026464.1,                                                                                                                                                                       |
| AK026649.1, AF044323.1, S77771.1, AK024538.1, BC008196.1, AL133067.1, BC003683.1,                                                                                                 |
| BC008649.1, AK026528.1, BC008416.1, AB048913.1, AL049382.1, AK027173.1, AK026797.1,                                                                                               |
| AK000421.1,                                                                                                                                                                       |
| AK026462.1, BC002688.1, Y16645.1, AL050024.1, Y10936.1, AK026642.1, AK025084.1,                                                                                                   |
| AK000083.1, AB052191.1, AB055368.1, BC006525.1, AF081571.1, AK027111.1, S61953.1,                                                                                                 |
| AF090934.1, BC008387.1, AL136615.1, BC008284.1, AL136786.1, BC004530.1, AF110640.1,                                                                                               |
| AF159615.1, AF106697.1, AB063079.1, AL512689.1, BC003590.1, AL157482.1, AL050393.1,                                                                                               |
|                                                                                                                                                                                   |
| AL133062.1, U72621.3, BC004960.1, AB049849.1, AL136640.1, AB047623.1, AK024747.1,                                                                                                 |
| BC002409.1, AK025375.1, AF232009.1, AF217987.1, AK025092.1, AK025491.1, AL080162.1,                                                                                               |
| BC003548.1, BC002473.1, AK000647.1, BC002844.1, AY033593.1, AL137480.1, AK026506.1,                                                                                               |
| AL162004.1, AK024546.1, BC007499.1, BC005002.1, BC008673.1, AL512718.1, AB060897.1,                                                                                               |
| AK027161.1, AF202636.1, BC000090.1, AF061795.1, AK026452.1, AF151685.1, AL136754.1,                                                                                               |
| BC003684.1, AF260566.1, AK000391.1, AL353956.1, AL136586.1, BC005997.1, AL136784.1,                                                                                               |
| AL133560.1, AK026408.1, BC007053.1, AK024588.1, AK027096.1, BC006091.1, AL357195.1,                                                                                               |
| AF218014.1, AK025857.1, AB060879.1, AK026749.1, AK000257.1, BC007680.1, AL137558.1,                                                                                               |
| AL583915.1, AL117432.1, AL389982.1, S78214.1, AK024992.1, AB051158.1, AL389939.1,                                                                                                 |
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| HTLEPS   23   847000   1-1884   15-189                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |     |        |          |           | Mosteys71, AL10821, AL086741, AB06041, AR056611, AR056242, BC007325, AB060407, AL15869, AB0608031, AT132661, AB0608073, AT132661, AT137681, AT137681, AT137681, AT137681, AT137681, AT101581, AT101581, AT101581, AT101581, AT101581, AT101581, AT101581, AT137811, AT101581, ATT101581, ATT10158 |
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| 238 634852 1-804 15-818                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HTELS08 | 237 | 847090 | 1 - 1884 | 15 - 1898 | AW664990, AA608835, BE972717, AA383680, AW572898, AI028204, AI554902, AI138881.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Al561201, BP92684, AWATORO, AV7660019, AWATORO,  | HTLEP53 | 238 | 634852 | 1 - 804  | 15 - 818  | BF876683, AI755202, AI066646, AW613805, AA084609, AW769151, BE169870, AA601674,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alica   Alic   |         |     |        |          |           | AIS61210, BF926568, AW265614, BF826830, AI613389, AL042667, AL042670, AW130427,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| AVASSA9, AIN ARONA, AMA SON AL SELVANE BEDSON, ANY ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SELVANE AND ARONA SERVANE A |         |     |        |          |           | AI340151, AI859834, AW328202, AV754716, AW501278, BG222269, AI955029, AL134440, AI799569,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| PS-2717   PE-250-64, AVA18380, AVA18486, D97421, AV019504, AV02715, AV019504, AV02715, AV019504, AV02715, AV019504, AV02716, AV027216, AV027216, AV027216, AV027216, AV027216, AV027216, AV027216, AV02   |         |     |        |          |           | BG250286, AW518050, AW576457, BF725884, BE396158, AW974565, 105118, AA524616, AI732682, AV526750, AT105440, AA560741, AW756050, PF67403, AW758541, BE304069, A066719                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| ACORRESA, ACORPATE, ACORRESA, ACORRESA, ACORRESA, ALDROPROS, ACORRESA, ACORR |         |     |        |          |           | AW200329, AH22440, AA009/41, AW100920, D36/62, AL033493, AW230341, BE3U1006, AL933/16,   BE033170 BE576064 AW438850 AW438657 11057471   ACD10205 4 ACD27125 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| ACORRESPO, A. LASSONI, D. A. LASSONI, D. A. COROSTOZ, A. CAROSTOZ, A. CAROSZOZ, A. CALIZIBO, A. CAROBRELI, A. CALIZIBO, A. CAROBRELI, A. CAROBRERI, A. CAROBRELI, A. CAROB |         |     |        |          |           | AL356299.16. AC007216.2. AC008649.6. AC005484.2. AC005098.2. AC005740.1. AB020868.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| ZSSW13, ALDORS12, ALLIGRS2, ADJAGON; A PRODUCTS1, ALDORS763, ALGORGES     ZSSW13, ALGORGES   ALGORGES   ADJAGON; A PRODUCTS1, ADDORS964, ACOUGHS5, ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ACOUGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ACOUGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ACOUGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES   ALGORGES   ALGORGES     ALGORGES   ALGORGES   ALGORGES    |         |     |        |          |           | AC008569.6, AL359091.10, AL136527.9, AC005527.3, AC005000.2, AC005529.7, AL121809.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Z688713, AL153299, ACORSTON, AL0001324, ACORSTON, ACOR   |         |     |        |          |           | AC090883.1, AC006312.8, AC004166.12, AF250325.1, AL008726.3, AL139396.17, AC010913.9,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| ALLISBIES, ALLISSOS, ACOURSEYS, ALLIGEOVA, ENORSEZOL, ACOURSESIZ,  |         |     |        |          |           | Z85987.13, AL590762.1, AL121658.2, AJ246003.1, AP001781.4, AP001694.1, AC004867.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| AC005229, AC004092, AL4574515, AC00412, AC00722, AC009607, AL575755, AC00722, AC007224, AC00722, AC009607, AL575755, AC00725, AC009607, AL575755, AC00526, AC009601, AL57575, AC00726, AC00571, AC00721,  |         |     |        |          |           | AC011485.6, AF111167.2, AC002544.1, AC004702.1, AL158141.14, AC005071.2, AC007191.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC0058946, AC0004092, AC0040052, AC00040612, AC0009612, AC00731, AC002554 AC0058246, AC0070524, AC0050524, AL0550711, AP005102, AC007731, AC002751, AC007751, AC005751, AC005751, AC005751, AC007751,          |     |        |          |           | AC005229.1, AL357515.26, AC010412.7, AL161670.4, AF196972.1, AL135927.14, AC007227.3,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC008921, AC000824, AC000824, AC008824, AC008912, AC009731, 4, AC007731, 4, AC007731, 4, AC007731, 4, AC007731, 4, AC007731, 4, AC007721,          |     |        |          |           | AC083884.6, AC004089.25, AL445483.13, AF165926.2, AC009060.7, AL359235.3, AC002350.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| ALD1388-1, AC008-982, ALI617231, AC008-9014, AC008513, ALI61893-24, AC008-7024,          |     |        |          |           | AC005952.1, AC007052.4, AC020558.4, AL035071.17, AP000510.2, AC007731.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AUG05214, AUG08522, AUG01875, AUG052501, AUG05251, AUG052515, AUG05252, AUG0 |         |     |        |          |           | AL121586.31, AL354815.10, AC005500.2, AC006014.2, AC005015.2, AL161893.24,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| ALO1397, ACOURSES, ACOURTES, ALUSSE, ALUSSES, ACOURTSS, ALUSSES, ACUSTSSES, ALUSSES, ACUSTSSES, ACU |         |     |        |          |           | AL160231.4, AC026672.44, AC004466.1, AC060231.6, AL360227.17, AL117382.28,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AC004221, AL029091, AL029041, AC004821, AL029041, AC004231, AL029041, AC004221, AL029041, AC004221, AC004201, AC004201, AC00401, AC004201, AC00401, AC00401, AC00401, AC00401, AC00401, AC00401, AC00401, AC006401, AC06 |         |     |        |          |           | AL021397.1, AC083863.2, AC011487.5, AL158824.11, AC018638.5, AL031283.26, AL121761.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AC067941, AC0035121, AC015262, AC000381, AC006803, AC006033, AC006033, AC006033, AC006033, AC006033, AC006033, AC006033, AC006033, AC006312, AC0003811, AC0068812, AC0003812, AC003371, AC0036812, AC003371, AC0036812, AC0037312, AC0037312, AC0037312, AC003872, AC0037312, AC003 |         |     |        |          |           | AC004242.1, AL020993.1, AL512641.9, AL121936.17, AC005280.3, AL035587.5, AC020916.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL0893083, AC006531.1, AL0497763, AP000141.1, AC0068518, AL0316020, AL391827, AP0016084, AL038771, AC0016034, AL038771, AC0016034, AL038771, AC0016034, AL038771, AC0020346, AC0070346, AC0070347, AC00703473, AC0080343, AC0080344, AC0080346, AC |         |     |        |          |           | ACUG/941.1, ACUG/9612.1, ACUL24/0.9, ALI36220.9, ARUU1/29.1, ALI359606.24, ALI36261.16, ALI36206.14, ADMINISTRY ACUG/973.3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| AC002446, AL13872412, AL0352112, AC003066, AC0036452, AC007003, AC002442, AC007003, AC002413, AC002403, AC |         |     |        |          |           | AP001360,4, AL354707.17, AF111168.2, AL031683.2, U89337.1, AC010605.4, AL035367.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| AC0099424, AL00954710, ALIGREPS, AFRGERGI, AC000022, AC0027319, AC0097319, AC0097319, AC0097319, AC0097310, AC0097311, AC0097310, AC0097311, AC0097310, AC0097311, AC |         |     |        |          |           | AC002546.1, AL138724.12, AL033521.2, AC020906.6, AC078846.2, AC006452.4, AC007003.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL391290.15, AC0080812, AC0042551, AC0082982, AC0019641, AL4104976614, AL512666, AL5138784, AC0083772, AC009360.35, AC0083772, AC009360.35, AC008378, AC0093793, AC0093793, AC0093793, AC009374, AC0093793, AC0093773, AC0093793, AC0093773, AC009 |         |     |        |          |           | AC009244.24, AL049547.10, AL163279.2, AF064861.1, AC000025.2, AC027319.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL138784.3 AO088917. AC084373. AC08373. AC063572. AC06363. AC06369.7 AC06364.3 AC063673. AC06364.3 AC063673. AC06374.3 AC06374. AC06374.3 AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374. AC06374.  |         |     |        |          |           | AL391280.15, AC008083.23, AC004253.1, AC008598.5, Y10196.1, AL049766.14, AL512666.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL049637.43, AL512378.7, AC008753, AC005488.2, AF001548.1, AC01042.2.7, AC009179, AC008023.4, AC008623.4, AC0010479.1, AC008079.1, AC00807 |         |     |        |          |           | AL138784.30, AC008891.7, AC004840.3, AC083873.3, AC005377.2, AC000360.35,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AC008623.4 AC004847.5, AP0017171, AP01771.1, AP0177171, |         |     |        |          |           | AL049637.43, AL512378.7, AC008753.8, AC005488.2, AF001548.1, AC010422.7, AC009179.17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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652 A/                                                                                                     | 15-1711 AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| AD19624, T79760, AD26408, AA466570, BE743375, A679772, W25733, AD27666, E96470, AD19624, T79760, AD26408, AA466570, BE743375, A679772, W25733, AD27666, E96470, | HTTBS64                  | HISROGEN AARSTST, AARSTSTON, TALOGEN, INSOON, INSOON, INSOON, AARSTSTON, AAR |
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|                                                                                                                                                                 | 267 St 177 1 M180161 2MC | AAALSOUG BETOOSEA BETOOTS! AAACOTSO AROUTOSES!; ALUZINOS 1.<br>AAAASOU BETOOTSA BETOOTSIAA AAACOTSO AROUTOSES!; ALUZINOS 1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

| K01562.1, AL035087.20, US4680. 1. AL518347, BE77030, AL11682, BE51499, AL118845, BF880731, AA23698, AL14098, AW813468, BE84131, AW882445, AA222594, AA618239, AR32453, AL20443, BF988077, AL042692, BF98907, BE90413, AW882446, AG011622, H15570, Z43079, H15600, AW813319, H22799, Z39170, AA252414, F07601, F11158, DR5157, AA746484, H15901, P6825, W68008, AW813329, F03848, F01404, AA84451, AC0063293, AR0333031, BC006271. 1. | AND 1949-65, AWEYSTRAKE HEINGSHOE, MAKERORU A. MASSINGA, AWESTRAKE, MESSYSS, AMADELSE, SHEYSTRAKE, HEINGSHOE, AWESTRAKE, MAKERORU A. MAGINER, MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MAYOR A. MA |
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| 1 - 2384                                                                                                                                                                                                                                                                                                                                                                                                                             | 1- 96 - 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| 247                                                                                                                                                                                                                                                                                                                                                                                                                                  | 248                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| AND ACADEMI, AADDONG AAADBING AAABURGEA, AAGGORGA, AAGGO | AL 53224 A ATA1056 A AN 94244 BASKOR BBSSTGA, AND 1201 BEND 5979 AND 51816TR, AAA231107 BEGGGSA, AND 1233, AAXSBARF, AA459411, AND 1933, ALA2370, ALDA299, BEDG2993, ANZ76617, AAV99617, AAA66614, ALBA574, ANS 34008, ALDS 21797 AND 249415, ALS 5425, AND 5171 AND 5181 AND 5181, AND 51826, AND 51825, ARD 51825, AND 51825, AND 5181 AND 5181 BEDGLGQ, AND 5203, AND 5498, AND 5181, AND 51941, AND 51941, AND 5181, AND 5181, AND 5181, AND 5181, AND 51841, AND 5181, AND 51 |
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| 1-1401                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1-854                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| 249                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 250                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| HTXON32                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | HUFC130                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

| <ul> <li>HIGRER, A.MUSTISTA, ANURORGO, ALAUSTISTA, ANUROLEGA, ANUROSTOSI, ANUROLEGA, ANUROSTOSI, A</li></ul> | EITTORGON, AAGUSTA ISE, RODZITS, AAGUSTON, AAGUSTON, RELAGON, BERTSSET, AAGUSTON, AGUSTON, AAGUSTON, AAGUS |           |
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| AV740801, AV76490, BG249643, AV762098, AI270117, AW969629, AI732378, AW265385,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| A1963720, A1708009, A1530211, AU147104, AW475163, AA669840, AV735495, A1149478, AV763971,<br>AA581903, AV759518, AV760937, A1754955, AL041690, A1583283, AV710066, AV763550.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| BG236735, AU145314, AW502975, AV742057, BG167743, BF940837, AW193265, AV760777,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BF914859, BF918590, AF074667, AV763122, BF918640, BE908796, BG036337, AW513362,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AA491814, AV759362, BF725315, AV762050, AV763354, AW021583, BF919090, AI203955,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AWGO1755 A A6615252, AA4901825, D82542, AW76591, AB25120, AV78945, AV782467, AW76017, AW700175, A A671373, A A663310, AV7008770, BEEATO1 A A6710401 TAIAGS A A SEATOT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AW44160, Al61220, AV762139, BE253048, Al192631, A773286, AW02092, AA938105,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| AV733830, AF074677, AV652936, AW276817, BE872393, AW088846, AW438643, A1434695,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| A1345654, AW270270, A1610159, AW274346, AW265170, BF680041, BF854876, AA469451,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AIS89230, AAS84145, AW833862, BE047069, AIS70261, BF347740, AI619997, AW264934,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AL042420, BF475381, AW518220, BF942454, AV762009, AI708125, BF697673, AW148792,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BE29/262, AW78410, AU59605, A445/542, BF99/1286, BF8061/6, AV78410, AU15937,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| AW08952, BEIGHAN, AND TAZZ, AB5218, AW96491, AV 05225, AB09966, ADUH 106, F302.13, AA 402600 AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATO A AVTACATOR DEPARTMENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AAA-90006, AV (PAZZE, AAAA-1052), AV (1524), AV (1010), 1020/13/7, BY (1021), AV (1010), 1020/13/7, AV (1010), 1020/13/2, AV (1020), |
| BG250302, AV761786, BE393367, BB872630, AP063563, AV764241, AA601294, BB827410.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BF812839, AL119691, AV760378, AA177061, BG177715, BF674620, AI298710, AW169151,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| AAS02104, AI345681, AI345675, AA633798, AV761925, AA682912, BF965007, AV733710,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| BF680074, AV762768, AA579362, BE139146, BF217299, AV762111, AV764578, AL118559.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AB038653.1, AC020904.6, AC009497.3, AC006581.16, AF001549.1, AC004638.1, AC008267.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL121601.13, AL109865.36, AL356915.19, AC018809.4, AL163973.1, AC023908.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AC011465.4, AL160237.4, AP000459.3, AC005081.3, AC044797.5, AC009154.5, AP001760.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AL035367.5, AC007298.17, AL139350.17, AC006329.5, AC004019.20, AC006038.2,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AC011455.6, AC008616.6, AL354932.26, AC011461.4, AL161892.9, AC005911.6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AC008265.15, U80017.1, AP003357.2, U91323.1, AC018636.4, AC005562.1, AL096701.14,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AL080243, 21, AC011450, AL1333674, AL162488, 10, AL354720,14, AC020638,6,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AL138830.17, AL050318.13, AC005839.1, AP001687.1, AC009144.5, AC005041.2, Z99495.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AC002565.1, AC022007.3, AC018769.2, AP000031.1, AC008372.6, AC011811.42, AC008688.7,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC009298.3, AP000047.1, AL44522.9, AL163248.2, AL139113.21, AC006435.7, AL136219.17,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC011495.6, AC008562.4, AC022308.17, AC008537.5, AP001667.1, AL133399.1, AL353135.32,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| ALL18896, A.CO05666, I. ACO7388, A.CO066038, AP00015.1, AL445928, ACO66021.2, ACO66021.3,  |
| ZO90001, ACUO32222, ACUO47023.2, ACUO42312, ACUO4906312, ACUO490695.0, ACUO490703 ACUO4703.1 ACUO47003.1 ACUO47003.1 ACUO47003.1 ACUO4703.1 ACUO4703.1 ACUO4703.1 ACUO4703.1 ACUO4703.1 ACUO4703.1 ACUO4703.1 ACUO4703.1 ACU                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| AP001346.1, AL034380.26, AC016830.5, AC008403.6, AL049550.5, AC027644.9, AC011930.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AL109965.34, AC006241.1, AL049869.6, Z83844.5, Z98941.1, AL031283.26, AL159191.4,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| MORDOZICI, ACODOSPOS, ACOUSTOS, ALLOSSISTI, ACOUSTOS, 6, ACOUSTOS, | ARW98227, AW7717 AW78247A, AW18828, STEIL HOZ, AAR7172, AAR50841, AW72402, AW77170, AAR50846, AW724086, AW77208, AA64086, AA64089, AA784525, AA64089, AW76273, AA64084, AA64089, AA784525, AA64089, AW76273, AW76274, AA64089, AA78408, AW76275, AA78408, AA78675, AA78677, AA78675, AA78677, AA78675, AA78677, AA78677, AA78677, AA78677, AA78675, AA78677, AA786 |
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| Add 224, Add 224, Add 254, Add 256, Add 258, Add 256, Ber7544, Add 25174, BEG7274, AW90229, Add 124, BES9774, Add 125, BEG7274, AW90229, Add 124, Add 125, AW90229, Add 124, Add 125, A | 15.1138   AW035606, PR350070, DR35070, PR35070,  15 - 6729   BE97010,2 BE968719, BR982135, BR870739 & BG177864, AW06064, AX60202, BE358859, BG24828, AUG6870, AWW06390, BE321201, ALI19604, AW602481, BE356056, AW499534, AW601673, AH40547, AAA110795, BG002481, AW60164, BE9366234, AW501912, AW8002940, AW601042, AW501912, AW8002940, AW601071, AW602450, AW8002940, AW601042, AK80202, BR88052, BB383, AV721883, BG57707, AW662450, AW970671, AW466902, AR6892021, AW1167025, AUG70577, AUG70877, AW602450, AW601071, AW602450, AW6024 |
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| BGI66654, AI866770, AL041150, AW104141, AI800440, BE877904, BF086116, AI433590, BE069120,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| AA80b/20, BE/78423, BC180b02, ALU36b73, BC112426, AB99623, AV735734, AL214887,<br>AW827103, BG028116, BE964614, AIS39847, AI863191, AI254727, AL039086, AI445992, BF885081.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| A1345608, BG029667, A1345688, AW083573, A1572717, AL036631, BF816037, A1613038, AW834302,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| BF909758, AW026882, AL038445, AI868931, R36271, BF872365, BG110517, BG257547, BG164558,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| A1267454, A1581033, A1623941, A1568114, AW167918, AA743354, AV714798, AV757035,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| AW983829, BF794478, AJ223603.2, AF082889.1, AC018758.2, AL353940.1, BC006472.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| A11126/01, AFW018801, AL115/7531, AL15/241, AFW053521, AFZ62432/11, ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATT114001 AND ATTT114001 AND ATTTT114001 AND ATTTT114001 AND ATTTT114001 AND ATTTT114001 AND ATTTTT114001 AND ATTTTT114001 AND ATTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT |
| AB15/460(1), AF050191.1, AE11/455.1, AE000154.1, A726087.1, AR024556.1, BC0045/0.1, AB047941.1, AE389935.1, AE117460.1, BC002473.1, AE136845.1, BC006103.1, AE389939.1.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| AB050431.1, Z82022.1, ALS12733.1, BC003548.1, ALL22093.1, AB052191.1, AK026762.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| BC004899.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| AK024992.1, AK027081.1, AI299431.1, AK026626.1, BC008417.1, AL137550.1, AK025491.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AL359601.1, AL117578.1, AL136893.1, AL359618.1, U80742.1, AF111112.1, BC008387.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AK027096.1, AL133640.1, AF225424.1, AL137459.1, AF183393.1, BC004958.1, AB048975.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AB063079.1, AB056809.1, AB052200.1, AK026927.1, AF061943.1, AL096744.1, AF090901.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| AF057300.1, AF057299.1, X98834.1, AL133067.1, Y16645.1, AL133558.1, AK026528.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| AL38982.1, AL136805.1, AL050277.1, AR026504.1, AK025391.1, AR027121.1, AB048933.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| AC021325.5, AL51274.1, AB06304.1, AR02630.1, AL080234.1, AL16206.2.1, AL259620.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AB003100.1, BC001644.1, AB023361.1, AR0243/0.1, BC008963.1, AL339941.1, AB000912.1,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|         |     |        |         |                                     | BC003683.1, AB060897.1, AF143723.1, BC005168.1, AK026744.1, AL117416.1, BC004195.1,  |
|---------|-----|--------|---------|-------------------------------------|--------------------------------------------------------------------------------------|
|         |     |        |         |                                     | AK026784.1, AL122100.1, AL122118.1, AB056768.1, AY033593.1, BC007499.1, AL110280.1,  |
|         |     |        |         |                                     | AL133560.1, AL080124.1, AK026647.1, BC009033.1, AK024588.1, AK026086.1, AL049283.1,  |
|         |     |        |         |                                     | BC008899.1, AB048919.1, AK026959.1, AK000647.1, AB048974.1, AL136792.1, Z37987.1,    |
|         |     |        |         |                                     | AL137529.1, BC007680.1, BC006525.1, BC001056.1, AL050116.1, BC003684.1, AL137558. 1. |
| HWTBK81 | 258 | 460568 | 1 - 623 | IWTBK81 258 460568 1 - 623 15 - 637 | T89795, AW769449, AA774621, AA954176, BF879355, H04799, BF879528, BE394321, R39277,  |
|         |     |        |         |                                     | T89429, R42299, AA873122, AC009238.4, AC008268.3, AC016683, 7.                       |

## Description of Table 4

10.149] Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B.2, column 5. Column 1 provides the tissue/cell source identifier code disclosed in Table 1B.2, Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 5. Column 6. San 
| Vector       |         |         |                 |            |                   |           |               |                         |                       |                         |                       |       |        |               |                       |                |                       |       |                   |                  |              |                          |                             |                        |                              |                          |                        |                          |       |                              |
|--------------|---------|---------|-----------------|------------|-------------------|-----------|---------------|-------------------------|-----------------------|-------------------------|-----------------------|-------|--------|---------------|-----------------------|----------------|-----------------------|-------|-------------------|------------------|--------------|--------------------------|-----------------------------|------------------------|------------------------------|--------------------------|------------------------|--------------------------|-------|------------------------------|
| Disease      |         |         |                 |            |                   |           |               |                         |                       |                         |                       |       |        |               |                       |                |                       |       |                   |                  |              |                          |                             |                        |                              |                          |                        |                          |       |                              |
| Cell Line    |         |         |                 |            |                   |           |               |                         |                       |                         |                       |       |        |               |                       |                |                       |       |                   |                  |              |                          |                             |                        |                              |                          |                        |                          |       |                              |
| <u>Organ</u> |         |         |                 |            |                   |           |               |                         |                       |                         |                       |       |        |               |                       |                |                       |       |                   |                  |              |                          |                             |                        |                              |                          |                        |                          |       |                              |
| Tissue       | a Heart | a_Liver | a_mammary gland | a Prostate | a_small intestine | a Stomach | Blood B cells | Blood B cells activated | Blood B cells resting | Blood T cells activated | Blood T cells resting | brain | breast | breast cancer | Cell Line CAOV3       | cell line PA-1 | cell line transformed | colon | colon (9808co65R) | colon (9809co15) | colon cancer | colon cancer (9808co64R) | colon cancer 9809co14       | Donor II B Cells 24hrs | Donor II B Cells 72hrs       | Donor II B-Cells 24 hrs. | Donor II B-Cells 72hrs | Donor II Resting B Cells | Heart | Human Lung (clonetech)       |
| Description  | a Heart | a_Liver | a_mammary gland | a Prostate | a small intestine | a Stomach | Blood B cells | Blood B cells activated | Blood B cells resting | Blood T cells activated | Blood T cells resting | brain | breast | breast cancer | AR036 Cell Line CAOV3 | cell line PA-1 | cell line transformed | colon | colon (9808co65R) | colon (9809co15) | colon cancer | colon cancer (9808co64R) | AR044 colon cancer 9809co14 | Donor II B Cells 24hrs | AR051 Donor II B Cells 72hrs | Donor II B-Cells 24 hrs. | Donor II B-Cells 72hrs | Donor II Resting B Cells | Heart | AR056 Human Lung (clonetech) |
| Code         | AR022   |         | AR024           | AR025      | AR026             |           | AR028         | AR029                   | AR030                 |                         | AR032                 | AR033 |        | AR035         | AR036                 | AR037          |                       |       | AR040             | AR041            | AR042        | AR043                    | AR044                       | AR050                  | AR051                        | AR052                    | AR053                  |                          | AR055 | AR056                        |

|       |                                     |                                                             | ſ      |
|-------|-------------------------------------|-------------------------------------------------------------|--------|
| AR057 | AR057 Human Mammary (clontech)      | Human Mammary (clontech)                                    |        |
| AR058 | Human Thymus (clonetech)            | Human Thymus (clonetech)                                    |        |
| AR059 | Jurkat (unstimulated)               | Jurkat (unstimulated)                                       |        |
| AR060 | Kidney                              | Kidney                                                      |        |
| AR061 | Liver                               | Liver                                                       |        |
| AR062 | Liver (Clontech)                    | Liver (Clontech)                                            |        |
| AR063 | Lymphocytes chronic                 | Lymphocytes chronic hymphocytes chronic hymphocytes chronic | _      |
| AR064 | Lymphocytes diffuse large B         | Lymphocytes diffuse large B                                 | _      |
|       | cell lymphoma                       | cell lymphoma                                               | $\neg$ |
| AR065 | Lymphocytes follicular              | Lymphocytes follicular                                      | _      |
|       | lymphoma                            | lymphoma                                                    | $\neg$ |
| AR066 | normal breast                       | normal breast                                               |        |
| AR067 | Normal Ovarian (4004901)            | Normal Ovarian (4004901)                                    |        |
| AR068 | AR068   Normal Ovary 9508G045       | Normal Ovary 9508G045                                       |        |
| AR069 | AR069   Normal Ovary 9701G208       | Normal Ovary 9701G208                                       |        |
| AR070 | AR070   Normal Ovary 9806G005       | Normal Ovary 9806G005                                       | _      |
| AR071 | Ovarian Cancer                      | Ovarian Cancer                                              | _      |
| AR072 | Ovarian Cancer (9702G001)           | Ovarian Cancer (9702G001)                                   | г      |
| AR073 |                                     | Ovarian Cancer (9707G029)                                   |        |
| AR074 | AR074   Ovarian Cancer (9804G011)   | Ovarian Cancer (9804G011)                                   |        |
| _     | AR075   Ovarian Cancer (9806G019)   | Ovarian Cancer (9806G019)                                   |        |
| AR076 | AR076 Ovarian Cancer (9807G017)     | Ovarian Cancer (9807G017)                                   |        |
| AR077 | AR077 Ovarian Cancer (9809G001)     | Ovarian Cancer (9809G001)                                   |        |
| AR078 |                                     | ovarian cancer 15799                                        |        |
| AR079 | Ovarian Cancer 17717AID             | Ovarian Cancer 17717AID                                     |        |
| AR080 | Ovarian Cancer 4004664B1            | Ovarian Cancer 4004664B1                                    |        |
| AR081 | Ovarian Cancer 4005315A1            | Ovarian Cancer 4005315A1                                    |        |
| AR082 | AR082 ovarian cancer 94127303       | ovarian cancer 94127303                                     |        |
| AR083 | AR083 Ovarian Cancer 96069304       | Ovarian Cancer 96069304                                     |        |
| AR084 |                                     | Ovarian Cancer 9707G029                                     |        |
| AR085 | Ovarian Cancer 9807G045             | Ovarian Cancer 9807G045                                     |        |
| AR086 |                                     | ovarian cancer 9809G001                                     |        |
| AR087 |                                     | Ovarian Cancer 9905C032RC                                   |        |
| AR088 | AR088   Ovarian cancer 9907 C00 3rd | Ovarian cancer 9907 C00 3rd                                 |        |

| AR089 Pro<br>AR090 Pro<br>AR091 pro | Prostate                           | Prostate                                    |  |  |               |
|-------------------------------------|------------------------------------|---------------------------------------------|--|--|---------------|
| -                                   |                                    | 1 TOURISM                                   |  |  |               |
| Т                                   | Prostate (clonetech)               | Prostate (clonetech)                        |  |  |               |
| 1                                   | prostate cancer                    | prostate cancer                             |  |  |               |
| AR092 pro                           | prostate cancer #15176             | prostate cancer #15176                      |  |  |               |
| AR093 pro                           | prostate cancer #15509             | prostate cancer #15509                      |  |  |               |
| AR094 prc                           | AR094 prostate cancer #15673       | prostate cancer #15673                      |  |  |               |
| AR095 Srr.                          | AR095   Small Intestine (Clontech) | Small Intestine (Clontech)                  |  |  |               |
| AR096 Spleen                        | leen                               | Spleen                                      |  |  |               |
| AR097 Th                            | AR097 Thymus T cells activated     | Thymus T cells activated                    |  |  |               |
| AR098 Th                            | AR098   Thymus T cells resting     | Thymus T cells resting                      |  |  |               |
| AR099 To                            | Tonsil                             | Tonsil                                      |  |  |               |
| AR100 To                            | Tonsil geminal center              | Tonsil geminal center                       |  |  |               |
|                                     | centroblast                        | centroblast                                 |  |  |               |
| -                                   | Tonsil germinal center B cell      | Tonsil germinal center B cell               |  |  |               |
| AR102 To                            | Tonsil lymph node                  | Tonsil lymph node                           |  |  |               |
| AR103 To                            | Tonsil memory B cell               | Tonsil memory B cell                        |  |  |               |
| AR104 WI                            | Whole Brain                        | Whole Brain                                 |  |  | $\overline{}$ |
| AR105 Xe                            | Xenograft ES-2                     | Xenograft ES-2                              |  |  |               |
| AR106 Xe                            | AR106   Xenograft SW626            | Xenograft SW626                             |  |  |               |
| AR119 001: IL-2                     | 1: IL-2                            | 001: IL-2                                   |  |  |               |
| AR120 001: IL-2.1                   | 1: IL-2.1                          | 001: IL-2.1                                 |  |  |               |
| AR121 001: IL-2_b                   | 1: IL-2_b                          | 001: IL-2_b                                 |  |  | $\overline{}$ |
| AR124 002:                          | 002 : Monocytes untreated (1hr)    | 002 : Monocytes untreated (1hr)             |  |  |               |
| AR125 007                           | 002 : Monocytes untreated (5hrs)   | 002 : Monocytes untreated (5hrs)            |  |  |               |
| AR126 003                           | 002: Control.1C                    | 002: Control.1C                             |  |  | П             |
| AR127 002                           | 002: IL2.1C                        | 002: IL2.1C                                 |  |  |               |
| AR130 00:                           | 003 : Placebo-treated Rat          | 003 : Placebo-treated Rat<br>Lacrimal Gland |  |  |               |
| AR131 00                            | 003 - Placeho-treated Rat          | 003 : Placebo-freated Rat                   |  |  | Т             |
|                                     | Submandibular Gland                | Submandibular Gland                         |  |  |               |
| AR135 00-                           | 004 : Monocytes untreated (5hrs)   | 004 : Monocytes untreated (5hrs)            |  |  |               |
| AR136 004                           | 004 : Monocytes untreated          | 004 : Monocytes untreated 1hr               |  |  |               |

| AR139 |                                | 005: Placebo (48hrs)        |  |  |
|-------|--------------------------------|-----------------------------|--|--|
| AR140 | 006: pC4 (24hrs)               | 006: pC4 (24hrs)            |  |  |
| AR141 | 006: pC4 (48hrs)               | 006: pC4 (48hrs)            |  |  |
| AR152 | 007: PHA(1hr)                  | 007: PHA(1hr)               |  |  |
| AR153 | AR153 007: PHA(6HRS)           | 007: PHA(6HRS)              |  |  |
| AR154 | AR154 007: PMA(6hrs)           | 007: PMA(6hrs)              |  |  |
| AR155 | 008: 1449 #2                   | 008: 1449 #2                |  |  |
| AR161 | 01: A - max 24                 | 01: A - max 24              |  |  |
| AR162 | 01: A - max 26                 | 01: A - max 26              |  |  |
| AR163 | 01: A - max 30                 | 01: A - max 30              |  |  |
| AR164 | AR164 01: B - max 24           | 01: B - max 24              |  |  |
| AR165 | AR165 01: B - max 26           | 01: B - max 26              |  |  |
| AR166 | AR166 01: B - max 30           | 01: B - max 30              |  |  |
| AR167 | AR167 1449 Sample              | 1449 Sample                 |  |  |
| AR168 | AR168 3T3P10 1.0uM insulin     | 3T3P10 1.0uM insulin        |  |  |
| AR169 | 3T3P10 10nM Insulin            | 3T3P10 10nM Insulin         |  |  |
| AR170 | 3T3P10 10uM insulin            | 3T3P10 10uM insulin         |  |  |
| AR171 | 3T3P10 No Insulin              | 3T3P10 No Insulin           |  |  |
| AR172 |                                | 3T3P4                       |  |  |
| AR173 | AR173 Adipose (41892)          | Adipose (41892)             |  |  |
| AR174 | AR174 Adipose Diabetic (41611) | Adipose Diabetic (41611)    |  |  |
| AR175 | AR175 Adipose Diabetic (41661) | Adipose Diabetic (41661)    |  |  |
| AR176 | Adipose Diabetic (41689)       | Adipose Diabetic (41689)    |  |  |
| AR177 | Adipose Diabetic (41706)       | Adipose Diabetic (41706)    |  |  |
| AR178 | Adipose Diabetic (42352)       | Adipose Diabetic (42352)    |  |  |
| AR179 |                                | Adipose Diabetic (42366)    |  |  |
| AR180 | Adipose Diabetic (42452)       | Adipose Diabetic (42452)    |  |  |
| AR181 | Adipose Diabetic (42491)       | Adipose Diabetic (42491)    |  |  |
| AR182 | AR182 Adipose Normal (41843)   | Adipose Normal (41843)      |  |  |
| AR183 | Adipose Normal (41893)         | Adipose Normal (41893)      |  |  |
| AR184 | Adipose Normal (42452)         | Adipose Normal (42452)      |  |  |
| AR185 | Adrenal Gland                  | Adrenal Gland               |  |  |
| AR186 | Adrenal Gland + Whole Brain    | Adrenal Gland + Whole Brain |  |  |
| AR187 | B7(1hr)+ (inverted)            | B7(1hr)+ (inverted)         |  |  |
| AR188 | AR188   Breast (18275A2B)      | Breast (18275A2B)           |  |  |

| AR189 | Breast (4004199)                   | Breast (4004199)             |  |
|-------|------------------------------------|------------------------------|--|
| AR190 | Breast (4004399)                   | Breast (4004399)             |  |
| AR191 | Breast (4004943B7)                 | Breast (4004943B7)           |  |
| AR192 | Breast (4005570B1)                 | Breast (4005570B1)           |  |
| AR193 | AR193 Breast Cancer (4004127A30)   | Breast Cancer (4004127A30)   |  |
| AR194 | AR194 Breast Cancer (400443A21)    | Breast Cancer (400443A21)    |  |
| AR195 | AR195 Breast Cancer (4004643A2)    | Breast Cancer (4004643A2)    |  |
| AR196 | Breast Cancer (4004710A7)          | Breast Cancer (4004710A7)    |  |
| AR197 | Breast Cancer (4004943A21)         | Breast Cancer (4004943A21)   |  |
| AR198 | Breast Cancer (400553A2)           | Breast Cancer (400553A2)     |  |
| AR199 | Breast Cancer (9805C046R)          | Breast Cancer (9805C046R)    |  |
| AR200 | AR200 Breast Cancer (9806C012R)    | Breast Cancer (9806C012R)    |  |
| AR201 | AR201 Breast Cancer (OD 7 45913)   | Breast Cancer (ODQ 45913)    |  |
| AR202 | AR202 Breast Cancer (OD 245913)    | Breast Cancer (ODQ45913)     |  |
| AR203 | Breast Cancer (OD:)4591B)          | Breast Cancer (ODQ4591B)     |  |
| AR204 | Colon Cancer (15663)               | Colon Cancer (15663)         |  |
| AR205 |                                    | Colon Cancer (4005144A4)     |  |
| AR206 | Colon Cancer (4005413A4)           | Colon Cancer (4005413A4)     |  |
| AR207 | AR207 Colon Cancer (4005570B1)     | Colon Cancer (4005570B1)     |  |
| AR208 | AR208   Control RNA #1             | Control RNA #1               |  |
| AR209 | AR209 Control RNA #2               | Control RNA #2               |  |
| AR210 | AR210 Cultured Preadipocyte (blue) | Cultured Preadipocyte (blue) |  |
| AR211 | Cultured Preadipocyte (Red)        | Cultured Preadipocyte (Red)  |  |
| AR212 | Donor II B-Cells 24hrs             | Donor II B-Cells 24hrs       |  |
| AR213 |                                    | Donor II Resting B-Cells     |  |
| AR214 | H114EP12 10nM Insulin              | H114EP12 10nM Insulin        |  |
| AR215 | AR215 H114EP12 (10nM insulin)      | H114EP12 (10nM insulin)      |  |
| AR216 | AR216 H114EP12 (2.6ug/ul)          | H114EP12 (2.6ug/ul)          |  |
| AR217 | AR217 H114EP12 (3.6ug/ul)          | H114EP12 (3.6ug/ul)          |  |
| AR218 |                                    | HUVEC #1                     |  |
| AR219 | HUVEC #2                           | HUVEC #2                     |  |
| AR221 | L6 undiff.                         | L6 undiff.                   |  |
| AR222 | L6 Undifferentiated                | L6 Undifferentiated          |  |
| AR223 | AR223   L6P8 + 10nM Insulin        | L6P8 + 10nM Insulin          |  |
| AR224 | AR224 L6P8 + HS                    | SH + 8d9 I                   |  |

| AR225 L8F8 10HM HISHIRI<br>AR226 Liver (00-06-A007B) | LoPs 10nM Insulin<br>Liver (00-06-A007B) |   |  |
|------------------------------------------------------|------------------------------------------|---|--|
| AR227 Liver (96-02-A075)                             | Liver (96-02-A075)                       |   |  |
| AR228   Liver (96-03-A144)                           | Liver (96-03-A144)                       |   |  |
| AR229   Liver (96-04-A138)                           | Liver (96-04-A138)                       |   |  |
| AR230   Liver (97-10-A074B)                          | Liver (97-10-A074B)                      |   |  |
| AR231   Liver (98-09-A242A)                          | Liver (98-09-A242A)                      |   |  |
|                                                      | Liver Diabetic (1042)                    |   |  |
| AR233   Liver Diabetic (41616)                       | Liver Diabetic (41616)                   |   |  |
| AR234 Liver Diabetic (41955)                         | Liver Diabetic (41955)                   |   |  |
| AR235   Liver Diabetic (42352R)                      | Liver Diabetic (42352R)                  |   |  |
| AR236   Liver Diabetic (42366)                       | Liver Diabetic (42366)                   |   |  |
| AR237 Liver Diabetic (42483)                         | Liver Diabetic (42483)                   |   |  |
| AR238 Liver Diabetic (42491)                         | Liver Diabetic (42491)                   |   |  |
| AR239   Liver Diabetic (99-09-                       | Liver Diabetic (99-09-A281A)             | _ |  |
| AR240 Lung                                           | Lung                                     |   |  |
| AR241 Lung (27270)                                   | Lung (27270)                             |   |  |
| AR242   Lung (2727Q)                                 | Lung (2727Q)                             |   |  |
|                                                      | Lung Cancer (4005116A1)                  |   |  |
| AR244   Lung Cancer (4005121A5)                      | Lung Cancer (4005121A5)                  |   |  |
| AR245   Lung Cancer (4005121A5))                     | Lung Cancer (4005121A5))                 |   |  |
| AR246   Lung Cancer (4005340A4)                      | Lung Cancer (4005340A4)                  |   |  |
| AR247   Mammary Gland                                | Mammary Gland                            |   |  |
| AR248   Monocyte (CT)                                | Monocyte (CT)                            |   |  |
| AR249 Monocyte (OCT)                                 | Monocyte (OCT)                           |   |  |
| AR250   Monocytes (CT)                               | Monocytes (CT)                           |   |  |
| AR251 Monocytes (INFG 18 hr)                         | Monocytes (INFG 18 hr)                   |   |  |
| AR252 Monocytes (INFG 18hr)                          | Monocytes (INFG 18hr)                    |   |  |
| AR253 Monocytes (INFG 8-11)                          | Monocytes (INFG 8-11)                    |   |  |
| AR254 Monocytes (O CT)                               | Monocytes (O CT)                         |   |  |
| AR255 Muscle (91-01-A105)                            | Muscle (91-01-A105)                      |   |  |
| AR256   Muscle (92-04-A059)                          | Muscle (92-04-A059)                      |   |  |
| AR257   Muscle (97-11-A056d)                         | Muscle (97-11-A056d)                     |   |  |
| AR258   Muscle (99-06-A210A)                         | Muscle (99-06-A210A)                     |   |  |

|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          | Γ        |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Γ                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------|--------------------|--------------------|--------------|-------------------|-----------------|-----------------|-------|--------------------------|---------------------------|-----------------------|----------------------------|-------------------|-----------------------------|-----------------------------|-----------------|-----------------|---------------|----------|----------|------------|----------|----------|--------------|----------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          | -          |          |          |              |                |                    | _                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                   |                    |                    |              |                   |                 |                 | -     | _                        |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                   |                    |                    |              |                   |                 |                 |       |                          |                           |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                   |
| -A203B)           | c (42352R)         | ic (42366)         | ontrol       | ated 72hrs        | ated 72 hrs.    | (94-08-13009)   |       | nal (97-01-<br>1)        | nal (97-04-               | nal (97-06-           | nal (97-09-                | (1717AID)         | 905C023RC)                  | 905C032RC)                  | 8G045)          | 1G208)          | 6G005         | as       | 90       | ltrol      | 8F       | TC       | Gland        | fuscle         | (91-01-105)        | le (42180)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | e (42386)                                                                                                                                                                                                                                                                                                                                                                                                         |
| Muscle (99-7      | Muscle Diabeti     | Muscle Diabet      | NK-19 C      | NK-19 IL Tres     | NK-19 UK Trea   | Omentum Normal  |       | Omentum Norr<br>A039,    | Omentum Norr<br>A1140     | Omentum Norr<br>A1170 | Omentum Norr<br>B0040      | Ovarian Cancer    | Ovarian Cancer (9           | Ovarian Cancer (9           | Ovary (950)     | Ovary (970      | Ovary 980     | Pancre   | Placet   | rIL2 Cor   | RSS28    | RSS288   | Salivary (   | Skeletal N     | Skeletal Muscle (  | Skeletal Muse                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Skeletal Muscle (42386)                                                                                                                                                                                                                                                                                                                                                                                           |
| 18                | :352R)             | (366)              |              | 2hrs              | 72 hrs.         |                 |       | 97-01-                   | 97-04-                    | -90-76                | -60-76                     | (ITAID)           | -                           |                             | -               | -               |               | -        |          | -          |          | -        | -            | _              | -01-               | 180)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 386)                                                                                                                                                                                                                                                                                                                                                                                                              |
| uscle (99-7-A203) | uscle Diabetic (42 | uscle Diabetic (42 | K-19 Control | K-19 IL Treated 7 | K-19 UK Treated | mentum Normal ( | (600  | mentum Normal (<br>039A) | mentum Normal (:<br>114C) | mentum Normal (*)     | mentum Normal (*)<br>004C) | varian Cancer (17 | varian Cancer<br>905C023RC) | varian Cancer<br>905C032RC) | vary (9508G045) | vary (9701G208) | vary 9806G005 | ncreas   | accho    | L2 Control | SS288L   | SS288LC  | livary Gland | celetal Muscle | celetal Muscle (9) | celetal Muscle (42                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | AR286 Skeletal Muscle (42386)                                                                                                                                                                                                                                                                                                                                                                                     |
| AR260 M           | AR261 M            | AR262 M            | AR263 NI     | AR264 NI          | AR265 NF        | AR266 Or        | -1    |                          | AR268 Or<br>AJ            | AR269 Or              | AR270 Or<br>BC             | AR271 Ov          |                             | AR273 O                     | AR274 Ov        | AR275 Ov        | AR276 O       | AR277 Pa | AR278 PI | AR279 rII  | AR280 R5 | AR281 RS | AR282 Sa     | AR283 Sk       | AR284 Sk           | AR285 Sk                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | AR286 Sk                                                                                                                                                                                                                                                                                                                                                                                                          |
|                   |                    | 2                  |              | 2                 |                 | 9               | 2 × 4 | 2 2                      | 3 8 4                     |                       |                            |                   |                             |                             |                 |                 |               |          |          |            |          |          |              |                |                    | Muscle (947-42031)  Muscle Diabetic (4235R)  Muscle Diabetic (4235R)  Muscle Diabetic (4235R)  Muscle Diabetic (4235R)  Muscl Diabetic (42366)  Muscl | Muscle (987-7-A031)  Muscle Diabetic (4235R)  Muscle Diabetic (4235R)  Muscle Diabetic (4235R)  Muscle Diabetic (4235R)  Muscle Diabetic (4236R)  Muscle Diabetic (4236R)  Muscle Diabetic (4236R)  Muscle Diabetic (4236R)  Muscle Diabetic (4238R)  Muscle (4218R)  Muscle (4218R) |

|                         |                              |                                      |                                      |                               |                                  |                                     |                                     |                                     |                                     | 2                                 |                        |                 |         |                                   | 22                               |                    |                   |                        |                       |                  |                |                 |               |                |        |       |
|-------------------------|------------------------------|--------------------------------------|--------------------------------------|-------------------------------|----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|------------------------|-----------------|---------|-----------------------------------|----------------------------------|--------------------|-------------------|------------------------|-----------------------|------------------|----------------|-----------------|---------------|----------------|--------|-------|
| Skeletal Muscle (42461) | Skeletal Muscle (91-01-A105) | Skeletal Muscle (92-04-A059)         | Skeletal Muscle (96-08-A171)         | Skeletal Muscle (97-07-A190A) | Skeletal Muscle Diabetic (42352) | Skeletal Muscle Diabetic (42366)    | Skeletal Muscle Diabetic<br>(42395) | Skeletal Muscle Diabetic<br>(42483) | Skeletal Muscle Diabetic<br>(42491) | Skeletal Muscle Diabetic 42352    | Skeletal Musle (42461) | Small Intestine | Stomach | T-Cell + HDPBQ71.fc 1449<br>16hrs | T-Cell + HDPBQ71.fc 1449 6hrs    | T-Cell + IL2 16hrs | T-Cell + IL2 6hrs | T-Cell Untreated 16hrs | T-Cell Untreated 6hrs | T-Cells 24 hours | T-Cells 24 hrs | T-Cells 24 hrs. | T-Cells 24hrs | T-Cells 4 days | Thymus | TRE   |
| Skeletal Muscle (42461) | Skeletal Muscle (91-01-A105) | AR289   Skeletal Muscle (92-04-A059) | AR290   Skeletal Muscle (96-08-A171) | Skeletal Muscle (97-07-       | Skeletal Muscle Diabetic         | Skeletal Muscle Diabetic<br>(42366) | Skeletal Muscle Diabetic<br>(42395) | Skeletal Muscle Diabetic<br>(42483) | Skeletal Muscle Diabetic<br>(42491) | Skeletal Muscle Diabetic<br>42352 | Skeletal Musle (42461) | Small Intestine | Stomach | T-Cell + HDPBQ71.fc 1449<br>16hrs | T-Cell + HDPBQ71.fc 1449<br>6hrs | T-Cell + IL2 16hrs | T-Cell + IL2 6hrs | T-Cell Untreated 16hrs | T-Cell Untreated 6hrs | T-Cells 24 hours | T-Cells 24 hrs | T-Cells 24 hrs. | T-Cells 24hrs | T-Cells 4 days | Thymus | TRE   |
| AR287                   | AR288                        | AR289                                | AR290                                | AR291                         | AR292                            | AR293                               | AR294                               | AR295                               | AR296                               | AR297                             | AR298                  | AR299           | AR300   | AR301                             | AR302                            | AR303              | AR304             | AR306                  | AR307                 | AR308            | AR309          | AR310           | AR311         | AR312          | _      | AR314 |

| <del></del>                      | INEC                           |   |
|----------------------------------|--------------------------------|---|
| <del></del>                      |                                | _ |
|                                  | B lymphocyte,                  |   |
|                                  | (non-T; non-B)                 |   |
|                                  | 001 - 293 RNA (Vector Control) |   |
| H                                | 001: Control                   |   |
| L                                | 001: Control.1                 |   |
| ACON Acute Lymphocyte Leukenna A | Acute Lymphocyte Leukemia      |   |
| AR356 AML Patient #11            | AML Patient #11                |   |
| AR357 AML Patient #2             | AML Patient #2                 |   |
| AML Patient #2 SGAH              | AML Patient #2 SGAH            |   |
| AML Patient#2                    | AML Patient#2                  |   |
| Aorta                            | Aorta                          |   |
| B Cell                           | B Cell                         |   |
| B lymphoblast                    | B lymphoblast                  |   |
| B lymphocyte                     | B lymphocyte                   |   |
| B lymphocytes                    | B lymphocytes                  |   |
| AR365 B-cell                     | B-cell                         |   |
| AR366 B-Cells                    | B-Cells                        |   |
| AR367   B-Lymphoblast            | B-Lymphoblast                  |   |
| AR368 B-Lymphocytes              | B-Lymphocytes                  |   |
| Bladder                          | Bladder                        |   |
| Bone Marrow                      | Bone Marrow                    |   |
| Bronchial Epithelial Cell        | Bronchial Epithelial Cell      |   |
| Bronchial Epithelial Cells       | Bronchial Epithelial Cells     |   |
| Caco-2A                          | Caco-2A                        |   |
| Caco-2B                          | Caco-2B                        |   |
| Caco-2C                          | Caco-2C                        |   |
| AR376 Cardiac #1                 | Cardiac #1                     |   |
| AR377 Cardiac #2                 | Cardiac #2                     |   |
| Chest Muscle                     | Chest Muscle                   |   |
| Dendritic Cell                   | Dendritic Cell                 |   |
| Dendritic cells                  | Dendritic cells                |   |
| E.coli                           | E.coli                         |   |
| Epithelial Cells                 | Epithelial Cells               |   |

|       | ı                                     |                                |  |  |
|-------|---------------------------------------|--------------------------------|--|--|
| AR385 | Esophagus                             | Esophagus                      |  |  |
| AR386 | . FPPS                                | Sddd                           |  |  |
| AR387 | FPPSC                                 | OSddH                          |  |  |
| AR388 | HepG2 Cell Line                       | HepG2 Cell Line                |  |  |
| AR389 | AR389 HepG2 Cell line Buffer 1 hr.    | HepG2 Cell line Buffer 1 hr.   |  |  |
| AR390 | AR390   HepG2 Cell line Buffer 06 hr  | HepG2 Cell line Buffer 06 hr   |  |  |
| AR391 | AR391   HepG2 Cell line Buffer 24 hr. | HepG2 Cell line Buffer 24 hr.  |  |  |
| AR392 | HepG2 Cell line Insulin 01 hr.        | HepG2 Cell line Insulin 01 hr. |  |  |
| AR393 |                                       | HepG2 Cell line Insulin 06 hr. |  |  |
| AR394 |                                       | HepG2 Cell line Insulin 24 hr. |  |  |
| AR398 |                                       | HMC-1                          |  |  |
| AR399 | HMCS                                  | HMCS                           |  |  |
| AR400 | AR400 HMSC                            | HMSC                           |  |  |
| AR401 | AR401 HUVEC #3                        | HUVEC #3                       |  |  |
| AR402 | HUVEC #4                              | HUVEC #4                       |  |  |
| AR404 | KIDNEY NORMAL                         | KIDNEY NORMAL                  |  |  |
| AR405 | KIDNEY TUMOR                          | KIDNEY TUMOR                   |  |  |
| AR406 | KIDNEY TUMOR                          |                                |  |  |
|       |                                       |                                |  |  |
|       |                                       |                                |  |  |
| AR407 | Lymph Node                            | Lymph Node                     |  |  |
| AR408 | Macrophage                            | Macrophage                     |  |  |
| AR409 | Megakarioblast                        | Megakarioblast                 |  |  |
| AR410 | Monocyte                              | Monocyte                       |  |  |
| AR411 |                                       | Monocytes                      |  |  |
| AR412 | : Myocardium                          | Myocardium                     |  |  |
| AR413 | AR413 Myocardium #3                   | Myocardium #3                  |  |  |
| AR414 | AR414   Myocardium #4                 | Myocardium #4                  |  |  |
| AR415 | AR415 Myocardium #5                   | Myocardium #5                  |  |  |
| AR416 | NK                                    | NK                             |  |  |
| AR417 | NK cell                               | NK cell                        |  |  |
| AR418 | NK cells                              | NK cells                       |  |  |
| AR419 | NKYa                                  | NKYa                           |  |  |
| AR420 | NKYa019                               | NKYa019                        |  |  |
| AR421 | AR421 Ovarv                           | Ovarv                          |  |  |

| AD422      | Potiont #11                        | Patient #11             |              |               |
|------------|------------------------------------|-------------------------|--------------|---------------|
| AR423      | -                                  | Peripheral blood        |              |               |
| AR424      | AR424 Primary Adipocytes           | Primary Adipocytes      |              |               |
| AR425      | AR425 Promyeloblast                | Promyeloblast           |              |               |
| AR427      | RSSWT                              | RSSWT                   |              |               |
| AR428      | RSSWTC                             | RSSWTC                  |              |               |
| AR429      | SW 480(G1)                         | SW 480(G1)              |              |               |
| AR430      | SW 480(G2)                         | SW 480(G2)              |              |               |
| AR431      | SW 480(G3)                         | SW 480(G3)              |              |               |
| AR432      | AR432 SW 480(G4)                   | SW 480(G4)              |              |               |
| AR433      | AR433 SW 480(G5)                   | SW 480(G5)              |              |               |
| AR434      | AR434   T Lymphoblast              | T Lymphoblast           |              |               |
| AR435      | T Lymphocyte                       | TLymphocyte             |              |               |
| AR436      | -                                  | T-Cell                  |              |               |
| AR438      | T-Cell,                            | T-Cell,                 |              |               |
| AR439      | -                                  | T-Cells                 |              |               |
| AR440      | T-lymphoblast                      | T-lymphoblast           |              |               |
| AR441      |                                    | Th.1                    |              |               |
| AR442 Th 2 | Th 2                               | Th 2                    |              |               |
| AR443 Th1  | Th1                                | Thi                     |              |               |
| AR444      | Th2                                | Th2                     |              |               |
| H0004      | Human Adult Spleen                 | Human Adult Spleen      | Spicen       | Uni-ZAP XR    |
| H0007      | Human Cerebellum                   | Human Cerebellum        | Brain        | Uni-ZAP XR    |
| H0008      | Whole 6 Week Old Embryo            |                         |              | Uni-ZAP XR    |
| H0009      | Human Fetal Brain                  |                         |              | Uni-ZAP XR    |
| H0012      | Human Fetal Kidney                 | Human Fetal Kidney      | Kidney       | Uni-ZAP XR    |
| H0013      |                                    | Human 8 Week Old Embryo | Embryo       | Uni-ZAP XR    |
|            | +                                  |                         | 100000       |               |
| H0014      | $\rightarrow$                      | Human Gall Bladder      | Gall Bladder | Uni-ZAP XR    |
| H0015      | Human Gall Bladder, fraction<br>II | Human Gall Bladder      | Gall Bladder | Uni-ZAP XR    |
| H0016      | Human Greater Omentum              | Human Greater Omentum   | peritoneum   | Uni-ZAP XR    |
| H0017      | Human Greater Omentum              | Human Greater Omentum   | peritoneum   | Uni-ZAP XR    |
| H0022      | Jurkat Cells                       | Jurkat T-Cell Line      |              | Lambda ZAP II |
| H0024      | Human Fetal Lung III               | Human Fetal Lung        | Lung         | Uni-ZAP XR    |

| Uni-ZAP XR    | disease |           | Sk Muscle      | Epithelioid Sarcoma, muscle | H0086 Human epithelioid sarcoma  | 980   |
|---------------|---------|-----------|----------------|-----------------------------|----------------------------------|-------|
| Lambda ZAP II |         |           |                | Human Colon                 | Human Colon                      | H0085 |
|               |         |           |                |                             | MEMBKANE BOUND<br>POLYSOMES      |       |
| Uni-ZAP XR    |         |           |                | Jurkat Cells                | HUMAN JURKAT                     | H0083 |
| Uni-ZAP XR    |         |           | Skin           | Human Fetal Skin            | Human Fetal Epithelium<br>(Skin) | H0081 |
| Lambda ZAP II | discase |           | Thymus         | Human Thymus Tumor          | Human Thymus Tumor               | H0077 |
| Uni-ZAP XR    |         | Cell Line | Blood          | Activated T-Cells           | Human Activated T-Cells (II)     | H0075 |
|               |         |           |                |                             | Carcinoma                        |       |
| Uni-ZAP XR    | discase |           | Muscle         | Human Leiomyeloid Carcinoma | Human Leiomyeloid                | H0073 |
| Uni-ZAP XR    |         |           | Adrenal gland  | Human Infant Adrenal Gland  | Human Infant Adrenal Gland       | H0071 |
| Uni-ZAP XR    |         |           | Pancreas       | Human Pancreas              | Human Pancreas                   | H0070 |
| Uni-ZAP XR    |         | Cell Line | Blood          | Activated T-Cells           | Human Activated T-Cells          | 6900H |
| Uni-ZAP XR    | discase |           | Skin           | Human Skin Tumor            | Human Skin Tumor                 | 8900H |
| Uni-ZAP XR    |         |           | Thymus         | Human Thymus                | Human Thymus                     | H0063 |
| Lambda ZAP II | disease |           | Uterus         | Human Uterine Cancer        | Human Uterine Cancer             | H0059 |
| Uni-ZAP XR    |         |           |                |                             | Human Fetal Spleen               | H0057 |
|               |         |           |                | Endothelial Cells           | Endo. remake                     |       |
| Ifni-ZAP XR   |         |           | Umbilical vein | Human I Imbilical Vein      | Human Umbilical Vein             | H0056 |
| Uni-ZAP XR    |         |           | Brain          | Human Cerebellum            | Human Cerebellum                 | H0052 |
| Uni-ZAP XR    |         |           | Brain          | Human Hippocampus           | Human Hippocampus                | H0051 |
| Uni-ZAP XR    |         |           | Heart          | Human Fetal Heart           | Human Fetal Heart                | H0050 |
| Uni-ZAP XR    | disease |           | Uterus         | Human Endometrial Tumor     | Human Endometrial Tumor          | H0046 |
| Uni-ZAP XR    |         |           | Lung           | Human Adult Pulmonary       | Human Adult Pulmonary            | H0042 |
| Uni-ZAP XR    |         |           | Bone           | Human Fetal Bone            | Human Fetal Bone                 | H0041 |
| Uni-ZAP XR    | disease |           | Testis         | Human Testes Tumor          | Human Testes Tumor               | H0040 |
| Uni-ZAP XR    | disease |           | Pancreas       | Human Pancreas Tumor        | Human Pancreas Tumor             | H0039 |
| Uni-ZAP XR    |         |           | Testis         | Human Testes                | Human Testes                     | H0038 |
| Uni-ZAP XR    |         |           | Small Int.     | Human Adult Small Intestine | Human Adult Small Intestine      | H0036 |
| Uni-ZAP XR    |         |           |                | Human Pituitary             | Human Pituitary                  | H0033 |
| Uni-ZAP XR    |         |           | Prostate       | Human Prostate              | Human Prostate                   | H0032 |
| Uni-ZAP XR    |         |           | Placenta       | Human Placenta              | Human Placenta                   | H0031 |
| Uni-ZAP XR    |         |           |                |                             | Human Placenta                   | H0030 |
| Lambda ZAP II |         |           | Lymph Node     | Human Adult Lymph Node      | Human Adult Lymph Node           | H0025 |

| H0087 | Human Thymus                                | Human Thymus                                         |             |           |         | pBluescript   | _ |
|-------|---------------------------------------------|------------------------------------------------------|-------------|-----------|---------|---------------|---|
| 0600H | Human T-Cell Lymphoma                       | T-Cell Lymphoma                                      | T-Cell      |           | disease | Uni-ZAP XR    |   |
| 9600H | Human Parotid Cancer                        | Human Parotid Cancer                                 | Parotid     |           | disease | Lambda ZAP II | _ |
| _     | Human Adult Liver,<br>subtracted            | Human Adult Liver                                    | Liver       |           |         | Uni-ZAP XR    |   |
| H0100 | Human Whole Six Week Old<br>Embryo          | Human Whole Six Week Old<br>Embryo                   | Embryo      |           |         | Uni-ZAP XR    | _ |
| H0102 | Human Whole 6 Week Old<br>Embryo (II), subt | Human Whole Six Week Old<br>Embryo                   | Embryo      |           |         | pBluescript   |   |
| H0108 | Human Adult Lymph Node,<br>subtracted       | Human Adult Lymph Node                               | Lymph Node  |           |         | Uni-ZAP XR    | _ |
| Н     | Human Placenta, subtracted                  | Human Placenta                                       | Placenta    |           |         | pBluescript   | _ |
| H0112 | Human Parathyroid Tumor,<br>subtracted      | Human Parathyroid Tumor                              | Parathyroid |           |         | pBluescript   |   |
| H0122 | Human Adult Skeletal Muscle                 | Human Skeletal Muscle                                | Sk Muscle   |           |         | Uni-ZAP XR    |   |
| H0123 | Human Fetal Dura Mater                      | Human Fetal Dura Mater                               | Brain       |           |         | Uni-ZAP XR    |   |
| Н     | Human Rhabdomyosarcoma                      | Human Rhabdomyosarcoma                               | Sk Muscle   |           | disease | Uni-ZAP XR    |   |
| H0125 | Cem cells cyclohexamide<br>treated          | Cyclohexamide Treated Cem,<br>Jurkat, Raji, and Supt | Blood       | Cell Line |         | Uni-ZAP XR    |   |
| H0128 | Jurkat cells, thiouridine<br>activated      | Jurkat Cells                                         |             |           |         | Uni-ZAP XR    |   |
| H0130 | LNCAP untreated                             | LNCAP Cell Line                                      | Prostate    | Cell Line |         | Uni-ZAP XR    | _ |
| Н     | LNCAP + 0.3nM R1881                         | LNCAP Cell Line                                      | Prostate    | Cell Line |         | Uni-ZAP XR    |   |
| H0132 | LNCAP + 30nM R1881                          | LNCAP Cell Line                                      | Prostate    | Cell Line |         | Uni-ZAP XR    |   |
| H0134 | Raji Cells, cyclohexamide<br>treated        | Cyclohexamide Treated Cem,<br>Jurkat, Raji, and Supt | Blood       | Cell Line |         | Uni-ZAP XR    |   |
| H0135 | Human Synovial Sarcoma                      | Human Synovial Sarcoma                               | Synovium    |           |         | Uni-ZAP XR    | _ |
| H0136 | Supt Cells, cyclohexamide<br>treated        | Cyclohexamide Treated Cem,<br>Jurkat, Raji, and Supt | Blood       | Cell Line |         | Uni-ZAP XR    |   |
| H0139 | Activated T-Cells, 4 hrs.                   | Activated T-Cells                                    | Blood       | Cell Line |         | Uni-ZAP XR    |   |
| H0140 | Activated T-Cells, 8 hrs.                   | Activated T-Cells                                    | Blood       | Cell Line |         | Uni-ZAP XR    |   |
| H0141 | Activated T-Cells, 12 hrs.                  | Activated T-Cells                                    | Blood       | Cell Line |         | Uni-ZAP XR    |   |
| H0144 | Nine Week Old Early Stage<br>Human          | 9 Wk Old Early Stage Human                           | Embryo      |           |         | Uni-ZAP XR    |   |
| H0149 | 7 Week Old Early Stage<br>Human, subtracted | Human Whole 7 Week Old<br>Embryo                     | Embryo      |           |         | Uni-ZAP XR    |   |
| ı     |                                             |                                                      |             |           |         |               | 1 |

|                  | _                       |                           |                                          | _                                         | _                                         |                |                                    | _                                           | _                                          |                                      |                                      |                                     | _                 |                   |                   |                  |                                |                                |                                |                |                     |                                                      |
|------------------|-------------------------|---------------------------|------------------------------------------|-------------------------------------------|-------------------------------------------|----------------|------------------------------------|---------------------------------------------|--------------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------|-------------------|-------------------|-------------------|------------------|--------------------------------|--------------------------------|--------------------------------|----------------|---------------------|------------------------------------------------------|
| Uni-ZAP XR       | Uni-ZAP XR              | Uni-ZAP XR                | Uni-ZAP XR                               | Uni-ZAP XR                                | Uni-ZAP XR                                | Uni-ZAP XR     | Uni-ZAP XR                         | Uni-ZAP XR                                  | Uni-ZAP XR                                 | Uni-ZAP XR                           | Uni-ZAP XR                           | Lambda ZAP II                       | Uni-ZAP XR        | Uni-ZAP XR        | Uni-ZAP XR        | Uni-ZAP XR       | Uni-ZAP XR                     | Uni-ZAP XR                     | Uni-ZAP XR                     | Lambda ZAP II  | Uni-ZAP XR          | Uni-ZAP XR                                           |
|                  |                         | disease                   |                                          |                                           |                                           |                | discase                            | discase                                     | disease                                    |                                      |                                      |                                     |                   |                   |                   |                  | discase                        | discase                        | disease                        |                |                     |                                                      |
|                  |                         |                           | Cell Line                                | Cell Line                                 | Cell Line                                 |                |                                    |                                             |                                            |                                      |                                      |                                     | Cell Line         | Cell Line         |                   | Cell Line        |                                |                                |                                | Cell Line      |                     | Cell Line                                            |
| Testis           | Liver                   | Adrenal Gland             | Blood                                    | Blood                                     | Blood                                     | Synovium       | Prostate                           | Prostate                                    | Prostate                                   | Embryo                               | Embryo                               | Brain                               | Breast            | Breast            | Brain             | Blood            | Breast                         | Breast                         | Breast                         | Blood          | Breast              | Blood                                                |
| Epididymis       | Human Fetal Liver       | Human Adrenal Gland Tumor | Activated T-Cells                        | Activated T-Cells                         | Activated T-Cells                         | Human Synovium | Human Prostate Cancer, stage<br>B2 | Human Prostate Cancer, stage<br>B2          | Human Prostate Cancer, stage C             | Twelve Week Old Early Stage<br>Human | Twelve Week Old Early Stage<br>Human | Human Fetal Brain                   | CAMA1Ee Cell Line | CAMA1Ee Cell Line | Human Fetal Brain | Human Neutrophil | Human Primary Breast Cancer    | Human Primary Breast Cancer    | Human Primary Breast Cancer    | T-Cells        | Human Normal Breast | Cyclohexamide Treated Cem,<br>Jurkat, Raii, and Supt |
| Human Epididymus | Early Stage Human Liver | Human Adrenal Gland Tumor | Activated T-Cells, 8 hrs.,<br>ligation 2 | Activated T-Cells, 12 hrs.,<br>ligation 2 | Activated T-Cells, 24 hrs.,<br>ligation 2 | Human Synovium | Human Prostate Cancer, Stage<br>B2 | Human Prostate Cancer, Stage<br>B2 fraction | Human Prostate Cancer, Stage<br>C fraction | 12 Week Old Early Stage<br>Human     | 12 Week Old Early Stage<br>Human, II | Human Fetal Brain, random<br>primed | CAMA1Ee Cell Line | CAMA1Ee Cell Line | Human Fetal Brain | Human Neutrophil | Human Primary Breast<br>Cancer | Human Primary Breast<br>Cancer | Human Primary Breast<br>Cancer | Resting T-Cell | Human Normal Breast | Cem Cells, cyclohexamide<br>treated, subtra          |
| H0150            | H0151                   | H0156                     | H0159                                    | H0160                                     | H0161                                     | H0163          | H0165                              | H0166                                       | H0169                                      | H0170                                | H0171                                | H0172                               | H0176             | H0177             | H0178             | H0179            | H0180                          | H0181                          | H0182                          | H0187          | H0188               | H0192                                                |

| pBluescript                     | Uni-ZAP XR                          | pBluescript                       | pBluescript                           | pBluescript                  | pBluescript                | Uni-ZAP XR                  | pBluescript                                          | pBluescript                                          | Uni-ZAP XR                             | Uni-ZAP XR                              | Uni-ZAP XR                               | Uni-ZAP XR                                            | pBluescript              | pBluescript                                         | pBluescript                                                 | Uni-ZAP XR         | Uni-ZAP XR                                          | pBluescript                                         | Uni-ZAP XR              |
|---------------------------------|-------------------------------------|-----------------------------------|---------------------------------------|------------------------------|----------------------------|-----------------------------|------------------------------------------------------|------------------------------------------------------|----------------------------------------|-----------------------------------------|------------------------------------------|-------------------------------------------------------|--------------------------|-----------------------------------------------------|-------------------------------------------------------------|--------------------|-----------------------------------------------------|-----------------------------------------------------|-------------------------|
|                                 |                                     |                                   |                                       |                              |                            |                             |                                                      |                                                      |                                        |                                         |                                          |                                                       |                          |                                                     |                                                             | disease            |                                                     |                                                     |                         |
|                                 |                                     |                                   |                                       |                              |                            |                             | Cell Line                                            | Cell Line                                            | Cell Line                              | Cell Line                               | Cell Line                                | Cell Line                                             |                          |                                                     |                                                             |                    | Cell Line                                           |                                                     |                         |
| Brain                           | Heart                               | Colon                             | Lung                                  | Prostate                     | Prostate                   |                             | Blood                                                | Blood                                                | Blood                                  | Blood                                   | Blood                                    | Blood                                                 |                          | Heart                                               | Liver                                                       | Kidney             | Breast                                              | Heart                                               | Embryo                  |
| Human Cerebellum                | Human Cardiomyopathy                | Human Colon Cancer                | Human Fetal Lung                      | Human Prostate               | Human Prostate             | Human Pituitary             | Cyclohexamide Treated Cem,<br>Jurkat, Raji, and Supt | Cyclohexamide Treated Cem,<br>Jurkat, Raji, and Supt | Activated T-Cells                      | Activated T-Cells                       | Activated T-Cells                        | Activated T-Cells                                     | Human Colon              | Human Fetal Heart                                   | Human Colon Cancer,<br>metasticized to liver                | Human Kidney Tumor | C7MCF7 Cell Line, estrogen<br>treated               | Human Fetal Heart                                   | Human 8 Week Old Embryo |
| Human Cerebellum,<br>subtracted | Human Cardiomyopathy,<br>subtracted | Human Colon Cancer,<br>subtracted | Early Stage Human Lung,<br>subtracted | Human Prostate, differential | Human Prostate, subtracted | Human Pituitary, subtracted | Raji cells, cyclohexamide<br>treated, subtracted     | Supt cells, cyclohexamide<br>treated, subtracted     | Activated T-Cells, 0hrs,<br>subtracted | Activated T-Cells, 4 hrs,<br>subtracted | Activated T-Cells, 12 hrs,<br>subtracted | Activated T-Cells, 12hrs,<br>differentially expressed | Human Colon, subtraction | Human Fetal Heart,<br>Differential (Adult-Specific) | Human colon cancer,<br>metaticized to liver,<br>subtraction | Human Kidney Tumor | C7MCF7 cell line, estrogen<br>treated, Differential | Human Fetal Heart,<br>Differential (Fetal-Specific) | Human 8 Week Whole      |
| H0194                           | H0196                               | H0204                             | H0208                                 | H0211                        | H0212                      | H0213                       | H0214                                                | H0216                                                | H0218                                  | H0220                                   | H0224                                    | H0225                                                 | H0231                    | H0233                                               | H0235                                                       | H0239              | H0240                                               | H0242                                               | H0244                   |

| Cartilage<br>Bone<br>Testis<br>Lymph Node |
|-------------------------------------------|
| Lymph Node<br>Blood                       |
| Blood                                     |
| Colon                                     |
| Tonsil                                    |
| Blood                                     |
| Vein                                      |
| Vein                                      |
| Umbilical vein                            |
| Umbilical vein                            |
| Pancreas                                  |
| Blood                                     |
| Tonsil                                    |
| Spleen                                    |

|                                           |                     |                                       |                                                |                                      |                                              |                                               | _                            |                                     |                                      |                                     |                                     |                                          |                                                | _                     | _                    | _             |                          | _                    | _                     |                      |                                     |
|-------------------------------------------|---------------------|---------------------------------------|------------------------------------------------|--------------------------------------|----------------------------------------------|-----------------------------------------------|------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|-------------------------------------|------------------------------------------|------------------------------------------------|-----------------------|----------------------|---------------|--------------------------|----------------------|-----------------------|----------------------|-------------------------------------|
| pBluescript                               | ZAP Express         | Uni-ZAP XR                            | Uni-ZAP XR                                     | Uni-ZAP XR                           | Uni-ZAP XR                                   | Uni-ZAP XR                                    | Uni-ZAP XR                   | Uni-ZAP XR                          | Uni-ZAP XR                           | ZAP Express                         | ZAP Express                         | ZAP Express                              | Uni-ZAP XR                                     | Uni-ZAP XR            | pBluescript          | Uni-ZAP XR    | Uni-ZAP XR               | Uni-ZAP XR           | Uni-ZAP XR            | Uni-ZAP XR           | Uni-ZAP XR                          |
|                                           |                     |                                       |                                                |                                      |                                              |                                               |                              |                                     |                                      |                                     |                                     |                                          | disease                                        |                       | discase              |               | discase                  |                      |                       | discase              | disease                             |
|                                           | Cell Line           | Cell Line                             | Cell Line                                      | Cell Line                            | Cell Line                                    | Cell Line                                     | Cell Line                    | Cell Line                           | Cell Line                            |                                     |                                     |                                          |                                                |                       |                      |               |                          |                      |                       |                      |                                     |
| Adrenal gland                             | cell line           | Bone                                  | Bonc                                           | Bone                                 | Bone                                         | Bone                                          | Placenta                     | Placenta                            | Breast                               | Cord Blood                          | Cord Blood                          | Cord Blood                               | Synovium                                       | Brain                 |                      | Stomach       | Lymph Node               | Brain                | Brain                 | Ovary                | Skin                                |
| Human Infant Adrenal Gland                | K562 Cell line      | Human Osteoblastoma MG63<br>cell line | Human Ostcoblastoma MG63<br>cell line          | Human Ostcoblastoma HOS cell<br>line | Human Ostcoblastoma HOS cell<br>line         | Human Osteoblastoma HOS cell<br>line          | Amniotic Cells - TNF induced | Amniotic Cells - Primary<br>Culture | CAMA1Ee Cell Line                    | CD34 Positive Cells                 | CD34 Positive Cells                 | CD34 Depleted Buffy Coat<br>(Cord Blood) | Synovium, Chronic Synovitis/<br>Ostcoarthritis | Brain                 | pleural cancer       | Human Stomach | Human B Cell Lymphoma    | Human Frontal Cortex | Human Corpus Callosum | Ovarian Cancer       | Dermatofibrosarcoma<br>Protuberans  |
| Human Infant Adrenal Gland,<br>Subtracted | K562 + PMA (36 hrs) | Human OB MG63 control<br>fraction I   | Human OB MG63 treated (10<br>nM E2) fraction I | Human OB HOS control<br>fraction I   | Human OB HOS treated (1<br>nM E2) fraction I | Human OB HOS treated (10<br>nM E2) fraction I | Amniotic Cells - TNF induced | Amniotic Cells - Primary<br>Culture | HCBB"s differential<br>consolidation | CD34 positive cells (Cord<br>Blood) | CD34 positive cells (Cord<br>Blood) | CD34 depleted Buffy Coat<br>(Cord Blood) | Human Chronic Synovitis                        | human caudate nucleus | human pleural cancer | HUMAN STOMACH | HUMAN B CELL<br>LYMPHOMA | Human frontal cortex | human corpus colosum  | human ovarian cancer | Dermatofibrosarcoma<br>Protuberance |
| H0275                                     | H0280               | H0284                                 | H0286                                          | H0288                                | H0290                                        | H0292                                         | H0294                        | H0295                               | H0298                                | H0300                               | H0305                               | H0306                                    | H0309                                          | H0310                 | H0313                | H0316         | H0318                    | H0320                | H0327                 | H0328                | H0329                               |

| H0331 | Henatocellular Tumor                      | Henatocellular Tumor                   | Liver        |           | disease | Lambda ZAP II |
|-------|-------------------------------------------|----------------------------------------|--------------|-----------|---------|---------------|
| H0333 | Hemangiopericytoma                        | Hemangiopericytoma                     | Blood vessel |           | disease | Lambda ZAP II |
| H0334 | Kidney cancer                             | Kidney Cancer                          | Kidney       |           | disease | Uni-ZAP XR    |
| H0341 | Bone Marrow Cell Line<br>(RS4;11)         | Bone Marrow Cell Line RS4;11           | Bone Marrow  | Cell Line |         | Uni-ZAP XR    |
| H0343 | stomach cancer (human)                    | Stomach Cancer - 5383A<br>(human)      |              |           | discase | Uni-ZAP XR    |
| H0346 | Brain-medulloblastoma                     | Brain (Medulloblastoma)-<br>9405C006R  | Brain        |           | discase | Uni-ZAP XR    |
| H0350 | Human Fetal Liver, mixed 10<br>& 14 week  | Human Fetal Liver, mixed<br>10&14 Week | Liver        |           |         | Uni-ZAP XR    |
| H0351 | Glioblastoma                              | Glioblastoma                           | Brain        |           | disease | Uni-ZAP XR    |
| H0352 | wilm"s tumor                              | Wilm"s Tumor                           |              |           | discase | Uni-ZAP XR    |
| H0354 | Human Leukocytes                          | Human Leukocytes                       | Blood        | Cell Line |         | pCMVSport 1   |
| H0355 | H0355 Human Liver                         | Human Liver, normal Adult              |              |           |         | pCMVSport 1   |
| H0356 | H0356   Human Kidney                      | Human Kidney                           | Kidney       |           |         | pCMVSport 1   |
| H0357 | H0357 H. Normalized Fetal Liver, II       | Human Fetal Liver                      | Liver        |           |         | Uni-ZAP XR    |
| H0359 | KMH2 cell line                            | KMH2                                   |              |           |         | ZAP Express   |
| H0369 | H. Atrophic Endometrium                   | Atrophic Endometrium and<br>myometrium |              |           |         | Uni-ZAP XR    |
| H0370 | H. Lymph node breast Cancer               | Lymph node with Met. Breast<br>Cancer  |              |           | disease | Uni-ZAP XR    |
| H0373 | Human Heart                               | Human Adult Heart                      | Heart        |           |         | pCMVSport 1   |
| H0375 | Human Lung                                | Human Lung                             |              |           |         | pCMVSport 1   |
| H0379 | Human Tongue, frac 1                      | Human Tongue                           |              |           |         | pSport1       |
| H0380 | Human Tongue, frac 2                      | Human Tongue                           |              |           |         | pSport1       |
| H0381 | Bone Cancer                               | Bone Cancer                            |              |           | disease | Uni-ZAP XR    |
| H0383 | Human Prostate BPH, re-                   | Human Prostate BPH                     |              |           |         | Uni-ZAP XR    |
| H0384 | Brain, Kozak                              | Human Brain                            |              |           |         | pCMVSport 1   |
| H0386 | Leukocyte and Lung; 4<br>screens          | Human Leukocytes                       | Blood        | Cell Line |         | pCMVSport 1   |
| H0390 | Human Amygdala<br>Depression, re-excision | Human Amygdala Depression              |              |           | disease | pBluescript   |
| H0392 | H. Meningima, M1                          | Human Meningima                        | brain        |           |         | pSport1       |
| H0393 | Fetal Liver, subtraction II               | Human Fetal Liver                      | Liver        |           |         | pBluescript   |

| H0304 | A-14 cell line                                          | Dodd-Stemberg cell                       |                |           |         | 7 A D Evanges |
|-------|---------------------------------------------------------|------------------------------------------|----------------|-----------|---------|---------------|
| H0399 | Human Kidney Cortex, re-                                | Human Kidney Cortex                      |                |           |         | Lambda ZAP II |
|       | rescue                                                  |                                          |                |           |         |               |
| H0402 | CD34 depleted Buffy Coat<br>(Cord Blood), re-excision   | CD34 Depleted Buffy Coat<br>(Cord Blood) | Cord Blood     |           |         | ZAP Express   |
| H0404 | H. Umbilical Vein endothelial cells, uninduced          | HUVE Cells                               | Umbilical vein | Cell Line |         | Uni-ZAP XR    |
| H0405 | Human Pituitary, subtracted<br>VI                       | Human Pituitary                          |                |           |         | pBluescript   |
| H0406 | H Amygdala Depression,<br>subtracted                    | Human Amygdala Depression                |                |           |         | Uni-ZAP XR    |
| H0408 | Human kidney Cortex,<br>subtracted                      | Human Kidney Cortex                      |                |           |         | pBluescript   |
| H0409 | H. Striatum Depression,<br>subtracted                   | Human Brain, Striatum<br>Depression      | Brain          |           |         | pBluescript   |
| H0410 | H. Male bladder, adult                                  | H Male Bladder, Adult                    | Bladder        |           |         | pSport1       |
| H0411 | H Female Bladder, Adult                                 | Human Female Adult Bladder               | Bladder        |           |         | pSport1       |
| H0412 | Human umbilical vein<br>endothelial cells, IL-4 induced | HUVE Cells                               | Umbilical vein | Cell Line |         | pSport1       |
| H0413 | Human Umbilical Vein<br>Endothelial Cells, uninduced    | HUVE Cells                               | Umbilical vein | Cell Line |         | pSport1       |
| H0415 | H. Ovarian Tumor, II,<br>OV5232                         | Ovarian Tumor, OV5232                    | Ovary          |           | disease | pCMVSport 2.0 |
| H0416 | Human Neutrophils,<br>Activated, re-excision            | Human Neutrophil - Activated             | Blood          | Cell Line |         | pBluescript   |
| H0417 | Human Pituitary, subtracted<br>VIII                     | Human Pituitary                          |                |           |         | pBluescript   |
| H0418 | Human Pituitary, subtracted<br>VII                      | Human Pituitary                          |                |           |         | pBluescript   |
| H0421 | Human Bone Marrow, re-<br>excision                      | Вопе Матгоw                              |                |           |         | pBluescript   |
| H0422 | T-Cell PHA 16 hrs                                       | T-Cells                                  | Blood          | Cell Line |         | pSport1       |
| H0423 | T-Cell PHA 24 hrs                                       | T-Cells                                  | Blood          | Cell Line |         | pSport1       |
| H0424 | Human Pituitary, subt IX                                | Human Pituitary                          |                |           |         | pBluescript   |
| H0427 |                                                         | Human Adipose, left hiplipoma            |                |           |         | pSport1       |
| H0428 | Human Ovary                                             | Human Ovary Tumor                        | Ovary          |           |         | pSport1       |

|                                     |                                    |                                                                    |                         | _                         |                              |                                    | _                 | _                            |                                        |                                         | _                   |                                     | _                 | _                      | _                          |                                  | _                   | _                     |                                    |                          |                      | _                           | _                          |
|-------------------------------------|------------------------------------|--------------------------------------------------------------------|-------------------------|---------------------------|------------------------------|------------------------------------|-------------------|------------------------------|----------------------------------------|-----------------------------------------|---------------------|-------------------------------------|-------------------|------------------------|----------------------------|----------------------------------|---------------------|-----------------------|------------------------------------|--------------------------|----------------------|-----------------------------|----------------------------|
| ZAP Express                         | pBluescript                        | pBluescript                                                        | pCMVSport 2.0           | pSport1                   | Lambda ZAP II                | ZAP Express                        | pBluescript       | pBluescript                  | pSport1                                | pSport1                                 | pSport1             | pBluescript                         | pSport1           | pSport1                | pCMVSport 2.0              | pBluescript                      | pSport1             | pSport1               | pSport1                            | pSport1                  | pCMVSport 2.0        | pCMVSport 2.0               | pCMVSport 2.0              |
|                                     |                                    |                                                                    |                         |                           |                              |                                    |                   |                              | discase                                | disease                                 |                     |                                     |                   |                        |                            |                                  |                     |                       |                                    |                          | discase              | disease                     |                            |
| Cell Line                           |                                    | Cell Line                                                          |                         | Cell Line                 | Cell Line                    |                                    |                   |                              |                                        |                                         |                     |                                     |                   |                        |                            |                                  |                     |                       |                                    |                          |                      |                             |                            |
| cell line                           | Kidney                             | Umbilical vein                                                     | Ovary                   | Blood                     | Umbilical vein               |                                    |                   | Kidney                       | Splcen                                 | Spleen                                  |                     | Brain                               |                   |                        |                            | Kidney                           | Tonsil              | Salivary gland        |                                    |                          |                      |                             |                            |
| K562 Cell line                      | Kidney medulla                     | HUVE Cells                                                         | Ovarian Tumor, OV350721 | T-Cells                   | HUVE Cells                   | Human Whole Brain #2               | Eosinophils       | Kidney cortex                | Spleen, Metastic malignant<br>melanoma | Human Spleen, CLL                       | CD34 positive cells | Human Brain, Striatum<br>Depression | Human Eosinophils | CD34 positive cells    | CD34 positive cells        | Kidney medulla                   | Human Tonsil        | Human Salivary Gland  | Breast Cancer Cell line, MDA<br>36 | Breast Cancer Cell line, | Hodekin"s Lymphoma I | Hodgkin"s Lymphoma II       | Human Tonsils              |
| K562 + PMA (36 hrs),re-<br>excision | H. Kidney Medulla, rc-<br>excision | Human Umbilical Vein<br>Endothelial cells, frac B, re-<br>excision | Ovarian Tumor 10-3-95   | Resting T-Cell Library,II | H Umbilical Vein Endothelial | H. Whole Brain #2, re-<br>excision | Human Eosinophils | H. Kidney Cortex, subtracted | Spleen metastic melanoma               | Spleen, Chronic lymphocytic<br>leukemia | CD34+ cell, I       | H. Striatum Depression, subt        | Human Eosinophils | CD34+ cell, I, frac II | CD34+cells, II, FRACTION 2 | H. Kidney Medulla,<br>subtracted | Human Tonsil, Lib 3 | Salivary Gland, Lib 2 | Breast Cancer cell line, MDA<br>36 | Breast Cancer Cell line, | Hodgkin"s Lymphoma I | H0486 Hodgkin"s Lymphoma II | H0488 Human Tonsils, Lib 2 |
| H0429                               | H0431                              | H0433                                                              | H0435                   | H0436                     | H0437                        | H0438                              | H0439             | H0441                        | H0444                                  | H0445                                   | H0449               | H0455                               | H0457             | H0458                  | H0459                      | H0461                            | H0477               | H0478                 | H0483                              | H0484                    | H0485                | H0486                       | H0488                      |

| Crohn"s Disease                       | sease                                                     | Ileum                                                 | Intestine  |            | disease | pSport1       |
|---------------------------------------|-----------------------------------------------------------|-------------------------------------------------------|------------|------------|---------|---------------|
| HL-60, RA 4h, Subtracted              | Subtracted                                                | HL-60 Cells, RA stimulated for<br>4H                  | Blood      | Cell Line  |         | Uni-ZAP XR    |
| Keratinocyte                          |                                                           | Keratinocyte                                          |            |            |         | pCMVSport 2.0 |
| HEL cell line                         |                                                           | HEL cell line                                         |            | HEL 92.1.7 |         | pSport1       |
| Human Astrocyte                       | cyte                                                      | Human Astrocyte                                       |            |            |         | pSport1       |
| Ulcerative Colitis                    | olitis                                                    | Colon                                                 | Colon      |            |         | pSport1       |
| Liver, Hepatoma                       | oma                                                       | Human Liver, Hepatoma, patient                        | Liver      |            | discase | pCMVSport 3.0 |
| Human Liver, normal                   | er, normal                                                | Human Liver, normal, Patient #                        | Liver      |            |         | pCMVSport 3.0 |
| pBMC stin                             | pBMC stimulated w/ poly I/C                               | pBMC stimulated with poly I/C                         |            |            |         | pCMVSport 3.0 |
| NTERA2, control                       | control                                                   | NTERA2, Teratocarcinoma cell<br>line                  |            |            |         | pCMVSport 3.0 |
| NTERA2                                | NTERA2 + retinoic acid, 14                                | NTERA2, Teratocarcinoma cell                          |            |            |         | pSport1       |
| days                                  |                                                           | line                                                  |            |            |         |               |
| Primary D                             | Primary Dendritic Cells, lib 1                            | Primary Dendritic cells                               |            |            |         | pCMVSport 3.0 |
| Primary I                             | Primary Dendritic cells, frac 2                           | Primary Dendritic cells                               |            |            |         | pCMVSport 3.0 |
| PCR, pBN                              | PCR, pBMC I/C treated                                     | pBMC stimulated with poly I/C                         |            |            |         | PCRII         |
| Myoloid                               | Myoloid Progenitor Cell Line                              | TF-1 Cell Line; Myoloid<br>progenitor cell line       |            |            |         | pCMVSport 3.0 |
| Human D                               | Human Dermal Endothelial                                  | Human Dermal Endothelial                              |            |            |         | pSport1       |
| Cells,untreated                       | eated                                                     | Cells; untreated                                      |            |            |         |               |
| H. Primai<br>3                        | <ol> <li>H. Primary Dendritic Cells,lib</li> </ol>        | Primary Dendritic cells                               |            |            |         | pCMVSport 2.0 |
| Merkel Cells                          | ells                                                      | Merkel cells                                          | Lymph node |            |         | pSport1       |
| Pancreas                              | Pancreas Islet Cell Tumor                                 | Pancreas Islet Cell Tumour                            | Pancreas   |            | discase | pSport1       |
| T Cell helper                         | lper I                                                    | Helper T cell                                         |            |            |         | pCMVSport 3.0 |
| T cell helper II                      | per II                                                    | Helper T cell                                         |            |            |         | pCMVSport 3.0 |
| Human er<br>cells                     | Human endometrial stromal cells                           | Human endometrial stromal cells                       |            |            |         | pCMVSport 3.0 |
| Human endometra<br>cells-treated with | Human endometrial stromal<br>cells-treated with           | Human endometrial stromal<br>cells-treated with proge |            |            |         | pCMVSport 3.0 |
| progesterone                          | ne ,                                                      |                                                       |            |            |         |               |
| Human er<br>cells-treat               | Human endometrial stromal<br>cells-treated with estradiol | Human endometrial stromal<br>cells-treated with estra |            |            |         | pCMVSport 3.0 |
|                                       |                                                           |                                                       |            |            |         |               |

| _                  | _                       |                               | _               |                                          |                                                      |                                                 |                                           |                                            |                                       |                                                          | _                                                     |                                   |                                        |                                    | _                        | _                         |                                   |                                                     |                                                |
|--------------------|-------------------------|-------------------------------|-----------------|------------------------------------------|------------------------------------------------------|-------------------------------------------------|-------------------------------------------|--------------------------------------------|---------------------------------------|----------------------------------------------------------|-------------------------------------------------------|-----------------------------------|----------------------------------------|------------------------------------|--------------------------|---------------------------|-----------------------------------|-----------------------------------------------------|------------------------------------------------|
| pSport1            | pCMVSport 3.0           | pCMVSport 3.0                 | pCMVSport 3.0   | Uni-ZAP XR                               | pCMVSport 3.0                                        | pCMVSport 3.0                                   | ZAP Express                               | Uni-ZAP XR                                 | Uni-ZAP XR                            | pCMVSport 3.0                                            | pCMVSport 3.0                                         | Lambda ZAP II                     | Uni-ZAP XR                             | Lambda ZAP II                      | Lambda ZAP II            | Uni-ZAP XR                | Uni-ZAP XR                        | pCMVSport 3.0                                       | pCMVSport 3.0                                  |
|                    |                         |                               | disease         |                                          | disease                                              | disease                                         |                                           |                                            | disease                               | disease                                                  |                                                       | disease                           | disease                                |                                    |                          |                           |                                   | disease                                             | disease                                        |
|                    |                         |                               |                 | Cell Line                                |                                                      |                                                 |                                           |                                            |                                       |                                                          |                                                       |                                   |                                        |                                    |                          |                           |                                   |                                                     |                                                |
| Thymus             |                         | Вопе Маггоw                   | B Cell          | Blood                                    | groin                                                | groin                                           | Cord Blood                                | Small Int.                                 | T-Cell                                |                                                          |                                                       | Lung                              |                                        | Colon                              |                          | Stomach                   | Heart                             |                                                     |                                                |
| Fetal Thymus       | Pooled dendritic cells  | Нитап Вопе Матгом             | B Cell Lymphoma | Activated T-Cells                        | healing groin wound, 6.5 hours<br>post incision - 2/ | Groin-2/19/97                                   | CD34 Positive Cells                       | Human Adult Small Intestine                | T-Cell Lymphoma                       | HGS wound healing project;<br>abdomen                    | Olfactory epithelium from roof<br>of left nasal cacit | Human Lung Cancer                 | Stomach Cancer - 5383A<br>(human)      | Human Colon Cancer                 | Human Colon              | Human Stomach             | Human Adult Heart                 | Abdomen                                             | Abdomen                                        |
| Human Fetal Thymus | Dendritic cells, pooled | Human Bone Marrow,<br>treated | B Cell lymphoma | Activated T-Cells,12 hrs,re-<br>excision | Healing groin wound, 6.5<br>hours post incision      | Healing groin wound; 7.5<br>hours post incision | CD34 positive cells (cord<br>blood),re-ex | Human adult small<br>intestine,re-excision | Human T-cell lymphoma;re-<br>excision | Healing groin wound - zero hr<br>post-incision (control) | Olfactory<br>epithelium;nasalcavity                   | Human Lung Cancer,re-<br>excision | Stomach cancer (human);re-<br>excision | Human Colon Cancertre-<br>excision | Human Colon; re-excision | Human Stomach;re-excision | Human Adult Heart;re-<br>excision | Healing Abdomen<br>wound;70&90 min post<br>incision | Healing Abdomen Wound;15<br>days post incision |
| H0578              | H0580                   | H0581                         | H0583           | H0585                                    | H0586                                                | H0587                                           | H0589                                     | H0590                                      | H0591                                 | H0592                                                    | H0593                                                 | H0594                             | H0595                                  | 9650H                              | H0597                    | H0598                     | H0599                             | 0090Н                                               | H0601                                          |

| pBluescript                  | Uni-ZAP XR                                 | pCMVSport 1                         | pCMVSport 1                            | pCMVSport 1                        | pCMVSport 1                            | Uni-ZAP XR                         | Uni-ZAP XR               | Uni-ZAP XR                                | Uni-ZAP XR                                       | Uni-ZAP XR        | Uni-ZAP XR                        | Uni-ZAP XR                          | Uni-ZAP XR                                | Uni-ZAP XR                                  | pSportl                | pSport1                    | pSport1                                | Uni-ZAP XR                             | pSport1                                   | Lambda ZAP II            |
|------------------------------|--------------------------------------------|-------------------------------------|----------------------------------------|------------------------------------|----------------------------------------|------------------------------------|--------------------------|-------------------------------------------|--------------------------------------------------|-------------------|-----------------------------------|-------------------------------------|-------------------------------------------|---------------------------------------------|------------------------|----------------------------|----------------------------------------|----------------------------------------|-------------------------------------------|--------------------------|
|                              | disease                                    |                                     |                                        |                                    |                                        | discase                            |                          | disease                                   |                                                  |                   |                                   | discase                             |                                           |                                             |                        |                            |                                        |                                        |                                           |                          |
|                              |                                            |                                     |                                        |                                    |                                        |                                    |                          |                                           |                                                  |                   |                                   |                                     |                                           |                                             |                        |                            |                                        |                                        |                                           |                          |
|                              | Breast                                     |                                     |                                        |                                    |                                        | Ovary                              | Testis                   | Breast                                    | Testis                                           | Heart             | Kidney                            | Pancreas                            | Umbilical vein                            | Embryo                                      |                        |                            |                                        |                                        |                                           | Liver                    |
| Human Pituitary              | Human Primary Breast Cancer                | H,Leukocytes                        | H.Leukocytes                           | H.Leukocytes                       | H.Leukocytes                           | Ovarian Cancer                     | Human Testes             | Human Primary Breast Cancer               | Human Adult Testis                               | Human Fetal Heart | Human Fetal Kidney                | Human Pancreas Tumor                | Human Umbilical Vein<br>Endothelial Cells | Twelve Week Old Early Stage<br>Human        | Ku 812F Basophils      | Saos2 Cell Line; Untreated | Saos2 Cell Line; Vitamin D3<br>Treated | Human Pre-Differentiated<br>Adipocytes | Saos2 Cell Line;<br>Dexamethosome Treated | Hepatocellular Tumor     |
| Human Pituitary, re-excision | Human Primary Breast<br>Cancertre-excision | H. Leukocytes, normalized<br>cot 5A | H. Leukocytes, normalized<br>cot 500 B | H.Leukocytes, normalized cot<br>5B | H. Leukocytes, normalized<br>cot 500 A | Human Ovarian Cancer<br>Reexcision | Human Testes, Reexcision | Human Primary Breast<br>Cancer Reexcision | Human Adult Testes, Large<br>Inserts, Reexcision | Fetal Heart       | Human Fetal Kidney;<br>Reexcision | Human Pancreas Tumor;<br>Reexcision | Human Umbilical Vein;<br>Reexcision       | 12 Week Early Stage Human<br>II; Reexcision | Ku 812F Basophils Line | Saos2 Cells; Untreated     | Saos2 Cells; Vitamin D3<br>Treated     | Human Pre-Differentiated<br>Adipocytes | Saos2, Dexamethosome<br>Treated           | Hepatocellular Tumor,re- |
| H0604                        | 9090H                                      | H0610                               | H0611                                  | H0613                              | H0614                                  | H0615                              | H0616                    | H0617                                     | H0618                                            | H0619             | H0620                             | H0622                               | H0623                                     | H0624                                       | H0625                  | H0626                      | H0627                                  | H0628                                  | H0631                                     | H0632                    |

|       | avoicion                                                                           |                                                       |          |           |         |               | _ |
|-------|------------------------------------------------------------------------------------|-------------------------------------------------------|----------|-----------|---------|---------------|---|
| н0633 | Lung Carcinoma A549                                                                | TNFalpha activated A549Lung                           |          |           | disease | pSport1       | _ |
| H0634 | Human Testes Tumor, re-                                                            | Human Testes Tumor                                    | Testis   |           | disease | Uni-ZAP XR    | _ |
| H0635 | Human Activated T-Cells, re-<br>excision                                           | Activated T-Cells                                     | Blood    | Cell Line |         | Uni-ZAP XR    |   |
| Н0637 | Dendritic Cells From CD34<br>Cells                                                 | Dentritic cells from CD34 cells                       |          |           |         | pSport1       |   |
| H0638 | CD40 activated monocyte<br>dendridic cells                                         | CD40 activated monocyte dendridic cells               |          |           |         | pSport1       |   |
| H0640 | Ficolled Human Stromal<br>Cells, Untreated                                         | Ficolled Human Stromal Cells,<br>Untreated            |          |           |         | Other         | _ |
| H0641 | LPS activated derived<br>dendritic cells                                           | LPS activated monocyte derived dendritic cells        |          |           |         | pSport1       |   |
| H0642 | Hep G2 Cells, lambda library                                                       | Hep G2 Cells                                          |          |           |         | Other         | _ |
| H0643 | Hep G2 Cells, PCR library                                                          | Hep G2 Cells                                          |          |           |         | Other         |   |
| H0644 | Human Placenta (re-excision)                                                       | Human Placenta                                        | Placenta |           |         | Uni-ZAP XR    | _ |
| H0645 | Fetal Heart, re-excision                                                           | Human Fetal Heart                                     | Heart    |           |         | Uni-ZAP XR    | _ |
| H0646 | Lung, Cancer (4005313 A3):                                                         | Metastatic squamous cell lung                         |          |           |         | pSport1       | _ |
|       | Invasive Poorly Differentiated<br>Lung Adenocarcinoma,                             | carcinoma, poorly di                                  |          |           |         |               |   |
| H0647 | Lung, Cancer (4005163 B7):<br>Invasive, Poorly Diff.<br>Adenocarcinoma. Metastatic | Invasive poorly differentiated<br>lung adenocarcinoma |          |           | disease | pSport1       | _ |
| H0648 | Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot    | Papillary Cstic neoplasm of low<br>malignant potentia |          |           | disease | pSport1       |   |
| H0649 | Lung, Normal: (4005313 B1)                                                         | Normal Lung                                           |          |           |         | pSportl       | _ |
| H0650 | B-Cells                                                                            | B-Cells                                               |          |           |         | pCMVSport 3.0 |   |
| H0651 | Ovary, Normal: (9805C040R)                                                         | Normal Ovary                                          |          |           |         | pSport1       | _ |
| H0652 | Lung, Normal: (4005313 B1)                                                         | Normal Lung                                           |          |           |         | pSport1       |   |
| H0653 | Stromal Cells                                                                      | Stromal Cells                                         |          |           |         | pSport1       | _ |
| H0656 | B-cells (unstimulated)                                                             | B-cells (unstimulated)                                |          |           |         | pSport1       | _ |
| 557   | H0657 B-cells (stimulated)                                                         | B-cells (stimulated)                                  |          |           |         | pSport1       | _ |

| disease pSport1                                                      | disease pSport1                                           | disease pSport1                                           | disease pSport1              | pSport1                      | disease pSport1              | disease pSport1             | pSport1            | disease pSport1                      | pSport1                | pSport1                | pSport1                                           |                                    | pSport1                     | Uni-ZAP XR                                      | Uni-ZAP XR                                      | pCMVSport 3.0              | PCRII                 | Other                                     | pCMVSport 3.0                                      | pCMVSport 3.0                                            | pCMVSport 3.0           |
|----------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|------------------------------|------------------------------|------------------------------|-----------------------------|--------------------|--------------------------------------|------------------------|------------------------|---------------------------------------------------|------------------------------------|-----------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------|-----------------------|-------------------------------------------|----------------------------------------------------|----------------------------------------------------------|-------------------------|
| Ovary & Fallopian<br>Tubes                                           | Ovary                                                     |                                                           |                              | Breast                       | Breast                       | Breast                      |                    |                                      |                        |                        |                                                   |                                    | Ovary                       | Prostate                                        | Prostate                                        |                            |                       | Placenta                                  |                                                    |                                                          | Ovaries                 |
| 9809C332- Poorly differentiate                                       | Grade II Papillary Carcinoma,<br>Ovary                    | Poorly differentiated carcinoma,<br>ovary                 | Breast cancer                | Normal Breast - #4005522(B2) | Breast Cancer - #4005522(A2) | Breast Cancer               | Stromal cells 3.88 | Ovarian Cancer, Sample<br>#4004332A2 | Stromal cell(HBM 3.18) | stromal cell clone 2.5 | Ovarian Cancer - 4004650A3                        |                                    | Ovarian Cancer(4004576A8)   | Human Prostate Cancer, stage<br>B2              | Human Prostate Cancer, stage C                  | Colon Cancer 9808C064R     | B-Cells               | Placenta                                  | serous papillary adenocarcinoma<br>(9606G304SPA3B) | Serous papillary<br>adenocarcinoma, stage 3C<br>(9804G01 | Ovarian Cancer-9810G606 |
| Ovary, Cancer (9809C332):<br>Poorly differentiated<br>adenocarcinoma | Ovary, Cancer (15395A1F):<br>Grade II Papillary Carcinoma | Ovary, Cancer. (15799A1F) Poorly differentiated carcinoma | Breast, Cancer: (4004943 A5) | Breast, Normal: (4005522B2)  | Breast, Cancer: (4005522 A2) | Breast, Cancer: (9806C012R) | Stromal cells 3.88 | Ovary, Cancer: (4004332 A2)          | Stromal cells(HBM3.18) | stromal cell clone 2.5 | Ovary, Cancer(4004650 A3):<br>Well-Differentiated | Micropapillary Serous<br>Carcinoma | Ovary, Cancer: (4004576 A8) | Human Prostate Cancer, Stage<br>B2; re-excision | Human Prostate Cancer, Stage<br>C; re-excission | Colon, Cancer: (9808C064R) | TNFR degenerate oligo | screened clones from<br>placental library | Serous Papillary<br>Adenocarcinoma                 | Ovarian Serous Papillary<br>Adenocarcinoma               | Serous Papillary        |
| H0658                                                                | 6590H                                                     | 0990Н                                                     | H0661                        | H0662                        | E990H                        | H0664                       | E990H              | 9990H                                | L990H                  | 8990H                  | 0290H                                             |                                    | H0672                       | H0673                                           | H0674                                           | F10675                     | H0677                 | 8190H                                     | H0682                                              | H0683                                                    | H0684                   |

| H0685  | Adenocarcinoma of Ovary,<br>Human Cell Line, # OVCAR-<br>3 | Adenocarcinoma of Ovary,<br>Human Cell Line, # OVCAR-    |                |           |         | pCMVSport 3.0 |
|--------|------------------------------------------------------------|----------------------------------------------------------|----------------|-----------|---------|---------------|
| 9890H  | Adenocarcinoma of Ovary,<br>Human Cell Line                | Adenocarcinoma of Ovary,<br>Human Cell Line, # SW-626    |                |           |         | pCMVSport 3.0 |
| H0687  | Human normal<br>ovary(#9610G215)                           | Human normal<br>ovary(#9610G215)                         | Ovary          |           |         | pCMVSport 3.0 |
| H0688  | Human Ovarian<br>Cancen(#9807G017)                         | Human Ovarian<br>cancer(#9807G017),mRNA<br>from Manra Ru |                |           |         | pCMVSport 3.0 |
| 6890H  | Ovarian Cancer                                             | Ovarian Cancer, #9806G019                                |                |           |         | pCMVSport 3.0 |
| H0690  | H0690 Ovarian Cancer, # 9702G001                           | Ovarian Cancer, #9702G001                                |                |           |         | pCMVSport 3.0 |
| H0691  | Normal Ovary, #9710G208                                    | normal ovary, #9710G208                                  |                |           |         | pCMVSport 3.0 |
| H0693  | Normal Prostate<br>#ODQ3958EN                              | Normal Prostate Tissue #<br>ODQ3958EN                    |                |           |         | pCMVSport 3.0 |
| H0694  | Prostate gland<br>adenocarcinoma                           | Prostate gland, adenocarcinoma,<br>mod/diff, gleason     | prostate gland |           |         | pCMVSport 3.0 |
| H0695  | mononucleocytes from patient                               | mononucleocytes from patient at<br>Shady Grove Hospit    |                |           |         | pCMVSport 3.0 |
| 000N   | Human Hippocampus,<br>prescreened                          | Human Hippocampus                                        |                |           |         |               |
| S0001  | Brain frontal cortex                                       | Brain frontal cortex                                     | Brain          |           |         | Lambda ZAP II |
| S0002  | Monocyte activated                                         | Monocyte-activated                                       | poold          | Cell Line |         | Uni-ZAP XR    |
| S0003  | Human Osteoclastoma                                        | Osteoclastoma                                            | bone           |           | disease | Uni-ZAP XR    |
| S0004  | Prostate                                                   | Prostate BPH                                             | Prostate       |           |         | Lambda ZAP II |
| S0005  | Heart                                                      | Heart-left ventricle                                     | Heart          |           |         | pCDNA         |
| 9000S  | Neuroblastoma                                              | Human Neural Blastoma                                    |                |           | disease | pCDNA         |
| S0007  | Early Stage Human Brain                                    | Human Fetal Brain                                        |                |           |         | Uni-ZAP XR    |
| S0010  | Human Amygdala                                             | Amygdala                                                 |                |           |         | Uni-ZAP XR    |
| S0011  | STROMAL -<br>OSTEOCLASTOMA                                 | Osteoclastoma                                            | bone           |           | disease | Uni-ZAP XR    |
| \$0014 | Kidney Cortex                                              | Kidney cortex                                            | Kidney         |           |         | Uni-ZAP XR    |
| S0015  | Kidney medulla                                             | Kidney medulla                                           | Kidney         |           |         | Uni-ZAP XR    |
| S0016  |                                                            | Kidney pyramids                                          | Kidney         |           |         | Uni-ZAP XR    |
| S0022  | Human Osteoclastoma                                        | Osteoclastoma Stromal Cells                              |                |           |         | Uni-ZAP XR    |

|       | Stromal Cells - unamplified                |                                        |                           |           |         |             |
|-------|--------------------------------------------|----------------------------------------|---------------------------|-----------|---------|-------------|
| S0024 | Human Kidney Medulla -<br>unamplified      | Human Kidney Medulla                   |                           |           |         |             |
| S0026 | Stromal cell TF274                         | stromal cell                           | Bone marrow               | Cell Line |         | Uni-ZAP XR  |
| S0027 | Smooth muscle, serum treated               | Smooth muscle                          | Pulmanary artery          | Cell Line |         | Uni-ZAP XR  |
| 80028 | Smooth muscle, control                     | Smooth muscle                          | Pulmanary artery          | Cell Line |         | Uni-ZAP XR  |
| S0029 | brain stem                                 | Brain stem                             | brain                     |           |         | Uni-ZAP XR  |
| S0030 | Brain pons                                 | Brain Pons                             | Brain                     |           |         | Uni-ZAP XR  |
| S0031 | Spinal cord                                | Spinal cord                            | spinal cord               |           |         | Uni-ZAP XR  |
| S0032 | Smooth muscle-ILb induced                  | Smooth muscle                          | Pulmanary artery          | Cell Line |         | Uni-ZAP XR  |
| S0036 | Human Substantia Nigra                     | Human Substantia Nigra                 |                           |           |         | Uni-ZAP XR  |
| S0037 | Smooth muscle, IL1b induced                | Smooth muscle                          | Pulmanary artery          | Cell Line |         | Uni-ZAP XR  |
| S0038 | Human Whole Brain #2 -<br>Oligo dT > 1.5Kb | Human Whole Brain #2                   |                           |           |         | ZAP Express |
| 8003  | Hypothalamus                               | Hypothalamus                           | Brain                     |           |         | Uni-ZAP XR  |
| S0040 | Adipocytes                                 | Human Adipocytes from<br>Ostcoclastoma |                           |           |         | Uni-ZAP XR  |
| S0044 | Prostate BPH                               | prostate BPH                           | Prostate                  |           | disease | Uni-ZAP XR  |
| S0045 | Endothelial cells-control                  | Endothelial cell                       | endothelial cell-<br>lung | Cell Line |         | Uni-ZAP XR  |
| S0046 | Endothelial-induced                        | Endothelial cell                       | endothelial cell-<br>lung | Cell Line |         | Uni-ZAP XR  |
| 80048 | Human Hypothalamus,<br>Alzheimer's         | Human Hypothalamus,<br>Alzheimer"s     |                           |           | disease | Uni-ZAP XR  |
| S0049 | Human Brain, Striatum                      | Human Brain, Striatum                  |                           |           |         | Uni-ZAP XR  |
| 0500S | Human Frontal Cortex,<br>Schizophrenia     | Human Frontal Cortex,<br>Schizophrenia |                           |           | disease | Uni-ZAP XR  |
| S0051 | Human<br>Hypothalmus, Schizophrenia        | Human Hypothalamus,<br>Schizophrenia   |                           |           | disease | Uni-ZAP XR  |
| S0052 | neutrophils control                        | human neutrophils                      | poold                     | Cell Line |         | Uni-ZAP XR  |
| S0053 | Neutrophils IL-1 and LPS<br>induced        | human neutrophil induced               | poold                     | Cell Line |         | Uni-ZAP XR  |
| 9010S | STRIATUM DEPRESSION                        |                                        | BRAIN                     |           | disease | Uni-ZAP XR  |
| 0110S | Brain Amygdala Depression                  |                                        | Brain                     |           | disease | Uni-ZAP XR  |
| S0112 | Hypothalamus                               |                                        | Brain                     |           |         | Uni-ZAP XR  |
| S0114 | Anergic T-cell                             | Anergic T-cell                         |                           | Cell Line |         | Uni-ZAP XR  |

| Uni-ZAP XR  | pBluescript                | Uni-ZAP XR             | Uni-ZAP XR  | Uni-ZAP XR              | Uni-ZAP XR       | Lambda ZAP II | Uni-ZAP XR             | Uni-ZAP XR                         | Uni-ZAP XR                     | Uni-ZAP XR      | Uni-ZAP XR      | Uni-ZAP XR               | Uni-ZAP XR             | Uni-ZAP XR                               | pSport1                            | pSport1                        | pSport1              | pSportl                      | pBluescript                       | pSport1                 | pSport1                               | Uni-ZAP XR                           | Uni-ZAP XR                          | Uni-ZAP XR                    | ZAP Express                 |
|-------------|----------------------------|------------------------|-------------|-------------------------|------------------|---------------|------------------------|------------------------------------|--------------------------------|-----------------|-----------------|--------------------------|------------------------|------------------------------------------|------------------------------------|--------------------------------|----------------------|------------------------------|-----------------------------------|-------------------------|---------------------------------------|--------------------------------------|-------------------------------------|-------------------------------|-----------------------------|
|             | disease                    |                        |             |                         |                  |               |                        |                                    |                                |                 |                 |                          |                        | disease                                  |                                    |                                |                      |                              |                                   |                         |                                       | discase                              |                                     |                               |                             |
|             |                            | Cell Line              | Cell Line   |                         | Cell Line        | Cell Line     | Cell Line              | Cell Line                          |                                |                 |                 | Cell Line                |                        |                                          |                                    |                                |                      |                              | Cell Line                         |                         |                                       |                                      | Cell Line                           | Cell Line                     |                             |
| Вопе тапом  | bone                       | Pulmanary artery       | Knee        |                         |                  | Вопе тапом    | lung                   | poold                              |                                | Prostate        | prostate        | Prostate                 |                        |                                          |                                    |                                |                      |                              | Pulmanary artery                  |                         |                                       | bone                                 | poold                               |                               | Brain                       |
| Bone marrow | Osteoclastoma              | Smooth muscle          | Osteoblasts | Airway Epithelial       | apoptotic cells  | stromal cell  | cosinophil             | macrophage-oxidized LDL<br>treated | Macrophage (GM-CSF treated)    | prostate BPH    | Prostate        | LNCAP Cell Line          | PC3 prostate cell line | Bone Marrow Stroma, TNF &<br>LPS induced | Human Prostate BPH                 | Synovial Fibroblasts           | Synovial Fibroblasts | Synovial Fibroblasts         | Smooth muscle                     | Messangial cell         | Bone Marrow Stromal<br>Cell.intreated | Osteoclastoma                        | human neutrophil induced            | apoptotic cells               | Hypothalamus                |
| Bone marrow | Osteoclastoma-normalized A | Smooth muscle-edited A | Osteoblasts | Epithelial-TNFa and INF | Apoptotic T-cell | PERM TF274    | eosinophil-IL5 induced | Macrophage-oxLDL                   | Macrophage (GM-CSF<br>treated) | prostate-edited | Normal Prostate | LNCAP prostate cell line | PC3 Prostate cell line | Bone Marrow Stroma,<br>TNF&LPS ind       | Prostate BPH, Lib 2,<br>subtracted | Synovial Fibroblasts (control) | Synovial hypoxia     | Synovial IL-1/TNF stimulated | Smooth Muscle-HASTE<br>normalized | Messangial cell, frac 2 | Bone Marrow Stromal Cell,             | Human Osteoclastoma, re-<br>excision | Neutrophils IL-1 and LPS<br>induced | Apoptotic T-cell, re-excision | H. hypothalamus, frac A;re- |
| 80116       | S0122                      | S0124                  | 80126       | S0132                   | S0134            | S0136         | 80140                  | S0142                              | S0144                          | S0146           | 80148           | 80150                    | S0152                  | S0180                                    | S0190                              | S0192                          | 80194                | 9610S                        | S0206                             | 80210                   | S0212                                 | 80214                                | S0216                               | 80218                         | 80220                       |

| Uni-ZAP XR                                  | pSport1                                 | pCMVSport 2.0        | Uni-ZAP XR               | pSport1                              | Uni-ZAP XR                                    | Uni-ZAP XR                            | Lambda ZAP II                         | pSport1           | pSport1                       | Uni-ZAP XR                              | pSportl                             | pSport1                            | pSport1          | pSport1       | pSport1           | pSport1                                | pSport1                               | pSportl                                        | Uni-ZAP XR                             | Uni-ZAP XR                        | Uni-ZAP XR                 |
|---------------------------------------------|-----------------------------------------|----------------------|--------------------------|--------------------------------------|-----------------------------------------------|---------------------------------------|---------------------------------------|-------------------|-------------------------------|-----------------------------------------|-------------------------------------|------------------------------------|------------------|---------------|-------------------|----------------------------------------|---------------------------------------|------------------------------------------------|----------------------------------------|-----------------------------------|----------------------------|
| disease                                     |                                         | disease              |                          |                                      |                                               |                                       |                                       | disease           |                               |                                         | discase                             | discase                            | discase          |               |                   |                                        |                                       | disease                                        |                                        |                                   |                            |
|                                             |                                         |                      |                          |                                      |                                               |                                       |                                       |                   |                               |                                         |                                     |                                    |                  |               |                   |                                        |                                       |                                                |                                        | Cell Line                         |                            |
| Brain                                       |                                         | Femur                | spinal cord              | Synovial tissue                      |                                               |                                       | Brain                                 | Larynx,vocal cord | Вопе тапом                    | Brain                                   |                                     |                                    | Uvula            | Uvula         | Hypopharynx       |                                        |                                       |                                                |                                        | poold                             |                            |
| H. Brain, Frontal Cortex,<br>Epileptic      | Synovial Fibroblasts                    | Human Osteoblasts    | Spinal cord              | Synovial fobroblasts<br>(rheumatoid) | Macrophage (GM-CSF treated)                   | Human Adipose Tissue                  | Brain frontal cortex                  | Larynx tumor      | Bone marrow stroma, treatedSB | Frontal Lobe<br>dementia/Alzheimer"s    | Human ostcoarthritic cartilage      | Human osteoarthritic cartilage     | Palate carcinoma | Palate normal | Pharynx carcinoma | Human Normal Cartilage                 | Human Normal Cartilage                | Human osteoarthritic cartilage                 | Human Adipocytes from<br>Osteoclastoma | macrophage-oxidized LDL treated   | Amygdala                   |
| H. Frontal cortex,epileptic;re-<br>excision | Synovial Fibroblasts<br>(III/TNF), subt | Human Osteoblasts II | Spinal Cord, re-excision | Synovial hypoxia-RSF<br>subtracted   | H Macrophage (GM-CSF<br>treated), re-excision | Human Adipose Tissue, re-<br>excision | Brain Frontal Cortex, re-<br>excision | Larynx tumor      | Bone marrow stroma, treated   | Frontal lobe, dementia; re-<br>excision | Human osteoarthritic;fraction<br>II | Human osteoarthritis;fraction<br>I | Palate carcinoma | Palate normal | Pharynx carcinoma | Human Normal Cartilage<br>Fraction III | Human Normal Cartilage<br>Fraction IV | Human Osteoarthritic<br>Cartilage Fraction III | Adipocytes;re-excision                 | Macrophage-oxLDL; re-<br>excision | Human Amygdala;re-excision |
| S0222                                       | S0242                                   | 80250                | S0260                    | S0276                                | S0278                                         | S0280                                 | S0282                                 | S0294             | 80298                         | S0300                                   | S0312                               | S0314                              | 80328            | 80330         | S0332             | S0334                                  | S0336                                 | 80338                                          | S0342                                  | S0344                             | 80346                      |

| pSport1           | pSport1         | pSport1         | pSport1          | pSport1        | pSport1           | pSport1       | pSport1              |            | pSport1              | pSport1      | pSport1     | pSport1                 | Г                      | ZAP Express            | Uni-ZAP XR          |                                             | Uni-ZAP XR                              | pSport1                | pSport1         | pSport1        | pSport1        | pSport1       | pSport1       | pSport1       | Other                                     | Other                                | pCMVSport 3.0                | pSport1                    | pCMVSport 3.0                             |
|-------------------|-----------------|-----------------|------------------|----------------|-------------------|---------------|----------------------|------------|----------------------|--------------|-------------|-------------------------|------------------------|------------------------|---------------------|---------------------------------------------|-----------------------------------------|------------------------|-----------------|----------------|----------------|---------------|---------------|---------------|-------------------------------------------|--------------------------------------|------------------------------|----------------------------|-------------------------------------------|
| disease           |                 | disease         |                  | disease        |                   |               |                      |            | disease              |              | disease     |                         | discase                |                        | discase             |                                             | Cell Line                               |                        |                 |                |                |               |               |               | disease                                   |                                      |                              |                            |                                           |
| Hypopharynx       | Colon           | Colon           | Colon            | Colon          |                   |               |                      |            |                      |              |             |                         |                        | Brain                  |                     |                                             | Pulmanary artery                        |                        |                 |                |                |               |               |               |                                           |                                      |                              |                            |                                           |
| Pharynx carcinoma | Colon Normal    | Colon Carcinoma | Colon Normal     | Colon Tumor    | Quadriceps muscle | Soleus Muscle | Islets of Langerhans |            | Larynx carcinoma     | Normal colon | Colon Tumor | Pancreas Normal PCA4 No | Pancreas Tumor PCA4 Tu | Whole brain            | Human Hypothalamus. | Schizophrenia                               | Smooth muscle                           | Salivary gland; normal | Stomach; normal | Testis; normal | Rectum, normal | Rectum tumour | Colon, normal | Colon, tumour | Temporal cortex, alzheimer                | Hippocampus, Alzheimer<br>Subtracted | CHME Cell Line; treated      | CHME Cell line, untreatetd | Mo7e Cell Line GM-CSF treated<br>(1ng/ml) |
| Pharynx Carcinoma | Colon Normal II | Colon Carcinoma | Colon Normal III | Colon Tumor II | Human Quadriceps  | Human Soleus  | Human Pancreatic     | Langerhans | Larynx carcinoma III | Normal colon | Colon Tumor | Pancreas normal PCA4 No | Pancreas Tumor PCA4 Tu | Human Whole Brain, re- | Human               | Hypothalamus, schizophrenia,<br>re-excision | Smooth muscle, control; re-<br>excision | Salivary Gland         | Stomach;normal  | Testis; normal | Rectum normal  | Rectum tumour | Colon, normal | Colon, tumour | Temporal cortex-Alzheizmer;<br>subtracted | Hippocampus, Alzheimer<br>Subtracted | CHME Cell Line;treated 5 hrs | CHME Cell Line, untreated  | Mo7e Cell Line GM-CSF<br>treated (Ing/ml) |
| 80350             | S0354           | 80356           | 80358            | 80360          | 80364             | S0366         | 89808                |            | S0372                | 80374        | S0376       | 80378                   | 80380                  | 98£0S                  | 80388               |                                             | 80390                                   | S0392                  | 80394           | 80398          | S0404          | S0406         | 80408         | 80410         | S0412                                     | S0414                                | 80418                        | 80420                      | S0422                                     |

| S0424 | TF-1 Cell Line GM-CSF<br>Treated       | TF-1 Cell Line GM-CSF<br>Treated |                  |           |         | pSport1     |
|-------|----------------------------------------|----------------------------------|------------------|-----------|---------|-------------|
| S0426 | Monocyte activated; re-<br>excision    | Monocyte-activated               | poold            | Cell Line |         | Uni-ZAP XR  |
| S0428 | Neutrophils control; re-<br>excision   | human neutrophils                | poold            | Cell Line |         | Uni-ZAP XR  |
| S0430 | Aryepiglottis Normal                   | Aryepiglottis Normal             |                  |           |         | pSport1     |
| S0432 | Sinus piniformis Tumour                | Sinus piniformis Tumour          |                  |           |         | pSport1     |
| S0434 | Stomach Normal                         | Stomach Normal                   |                  |           | disease | pSport1     |
| S0436 | Stomach Tumour                         | Stomach Tumour                   |                  |           | disease | pSport1     |
| S0438 | Liver Normal Met5No                    | Liver Normal Met5No              |                  |           |         | pSport1     |
| S0440 | Liver Tumour Met 5 Tu                  | Liver Tumour                     |                  |           |         | pSport1     |
| S0442 | Colon Normal                           | Colon Normal                     |                  |           |         | pSport1     |
| S0444 | Colon Tumor                            | Colon Tumour                     |                  |           | disease | pSport1     |
| S0446 | Tongue Tumour                          | Tongue Tumour                    |                  |           |         | pSport1     |
| S0448 | Larynx Normal                          | Larynx Normal                    |                  |           |         | pSport1     |
| S0450 | Larynx Tumour                          | Larynx Tumour                    |                  |           |         | pSport1     |
| S0452 | Thymus                                 | Thymus                           |                  |           |         | pSport1     |
| S0454 |                                        | Placenta                         | Placenta         |           |         | pSport1     |
| S0456 | Tongue Normal                          | Tongue Normal                    |                  |           |         | pSport1     |
| S0458 | Thyroid Normal (SDCA2 No)              | Thyroid normal                   |                  |           |         | pSport1     |
| S0460 | Thyroid Tumour                         | Thyroid Tumour                   |                  |           |         | pSport1     |
| S0462 | Thyroid Thyroiditis                    | Thyroid Thyroiditis              |                  |           |         | pSport1     |
| S0470 | Adenocarcinoma                         | PYFD                             |                  |           | disease | pSport1     |
| S0472 | Lung Mesothelium                       | PYBT                             |                  |           |         | pSport1     |
| S0474 | Human blood platelets                  | Platelets                        | Blood platelets  |           |         | Other       |
| S0665 | Human Amygdala; re-<br>excission       | Amygdala                         |                  |           |         | Uni-ZAP XR  |
| S3012 | Smooth Muscle Serum<br>Treated, Norm   | Smooth muscle                    | Pulmanary artery | Cell Line |         | pBluescript |
| S3014 | Smooth muscle, serum<br>induced,re-exc | Smooth muscle                    | Pulmanary artery | Cell Line |         | pBluescript |
| S6014 | H. hypothalamus, frac A                | Hypothalamus                     | Brain            |           |         | ZAP Express |
| S6022 | H. Adipose Tissue                      | Human Adipose Tissue             |                  |           |         | Uni-ZAP XR  |
| S6024 | Alzheimers, spongy change              | Alzheimer"s/Spongy change        | Brain            |           | disease | Uni-ZAP XR  |

| Uni-ZAP XR                           | disease Uni-ZAP XR               | pBluescript SK-                | pBluescript SK- | pBluescript SK-     | pBluescriptISK-  | discase pBluescript SK- | Other              | disease pBluescript SK-    | pBluescript SK-        | pBluescript SK- | pBluescript SK-        | pBluescript SK-        | pBluescript SK-          | pBluescript SK-                    | pBluescript SK-     | pBluescript SK- | pBluescript SK-                | pBluescript SK-      | pBluescript SK-   | pBluescript SK-    | pBluescript SK-                          | pBluescript SK-             | pBluescript SK-                                           | pBluescript SK-                                  | pBluescript SK-                                               |
|--------------------------------------|----------------------------------|--------------------------------|-----------------|---------------------|------------------|-------------------------|--------------------|----------------------------|------------------------|-----------------|------------------------|------------------------|--------------------------|------------------------------------|---------------------|-----------------|--------------------------------|----------------------|-------------------|--------------------|------------------------------------------|-----------------------------|-----------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------|
|                                      |                                  | Cell Line                      |                 |                     |                  |                         |                    |                            |                        |                 |                        |                        |                          |                                    |                     |                 |                                |                      |                   |                    |                                          |                             |                                                           |                                                  |                                                               |
| Brain                                | Brain                            | Blood                          |                 |                     |                  |                         |                    |                            |                        |                 |                        |                        |                          |                                    |                     |                 |                                |                      |                   |                    |                                          |                             |                                                           |                                                  |                                                               |
| Frontal Lobe<br>dementia/Alzheimer"s | Human Manic depression tissue    | Activated T-Cell, PBL fraction | Human White Fat | Human Pinneal Gland | Colon Epithelium | Colorectal Tumor        | Human Infant Brain | Human Pancreatic Carcinoma | Human HSA172 cell line | SA172 Cells     | Jurkat T-cell          | Jurkat T-Cell Line     | Human Aortic Endothilium | Aorta endothelial cells            | Human White Fat     | Human Thyroid   | Normal Ovary, Premenopausal    | Human Uterus, normal | Human Bone Marrow | Human Adult Retina |                                          |                             |                                                           |                                                  |                                                               |
| Frontal Lobe, Dementia               | Human Manic Depression<br>Tissue | Activated T-cells              | Human White Fat | Human Pineal Gland  | Colon Epithelium | Colorectal Tumor        | Human Infant Brain | Human Pancreatic Carcinoma | T0039 HSA 172 Cells    | HSC172 cells    | Jurkat T-cell G1 phase | Jurkat T-Cell, S phase | Human Aortic Endothelium | Aorta endothelial cells +<br>TNF-a | Human White Adipose | Human Thyroid   | Normal Ovary,<br>Premenopausal | Human Uterus, normal | Human Bone Marrow | Human Adult Retina | Human colon carcinoma<br>(HCC) cell line | HCC cell line metastisis to | Human (HCC) cell line liver<br>(mouse) metastasis, remake | Human colon carcinoma<br>(HCC) cell line, remake | Human (Caco-2) cell line,<br>adenocarcinoma, colon,<br>remake |
|                                      | Se028                            | T0002                          |                 | T0006               |                  | T0008                   | T0010              | T0023                      | T0039                  | T0040           | T0041                  | T0042                  | T0048                    | T0049                              | T0060               | T0067           | T0068                          | T0069                | П                 | T0082              | T0103                                    | T0104                       | T0109                                                     | T0110                                            | T0114                                                         |

|       | tissue                                |                                                       |               |                |
|-------|---------------------------------------|-------------------------------------------------------|---------------|----------------|
| L0356 | S, Human foetal Adrenals              |                                                       |               | Bluescript     |
|       | tissue                                |                                                       |               |                |
| L0361 | Stratagene ovary (#937217)            |                                                       | ovary         | Bluescript SK  |
| L0362 | Stratagene ovarian cancer (#937219)   |                                                       |               | Bluescript SK- |
| L0363 | NCI CGAP GC2                          | gern cell tumor                                       |               | Bluescript SK- |
| L0364 | NCI CGAP GC5                          | germ cell tumor                                       |               | Bluescript SK- |
| L0366 | Stratagene schizo brain S11           | schizophrenic brain S-11 frontal                      |               | Bluescript SK- |
|       |                                       | lobe                                                  |               |                |
| L0367 | NCI_CGAP_Sch1                         | Schwannoma tumor                                      |               | Bluescript SK- |
| L0369 | L0369 NCI_CGAP_AA1                    | adrenal adenoma                                       | adrenal gland | Bluescript SK- |
| L0370 | Johnston frontal cortex               | pooled frontal lobe                                   | brain         | Bluescript SK- |
| L0371 | L0371   NCI_CGAP_Br3                  | breast tumor                                          | breast        | Bluescript SK- |
| L0372 | L0372 NCI CGAP Co12                   | colon tumor                                           | colon         | Bluescript SK- |
| L0373 |                                       | Jounn                                                 | uojoo         | Bluescript SK- |
| L0374 | NCI_CGAP_Co2                          | noun                                                  | uoloo         | Bluescript SK- |
| L0375 | NCI CGAP Kid6                         | kidney tumor                                          | kidney        | Bluescript SK- |
| L0376 | NCI_CGAP_Lar1                         | larynx                                                | larynx        | Bluescript SK- |
| L0378 | NCI_CGAP_Lu1                          | lung tumor                                            | hng           | Bluescript SK- |
| T0381 | NCI CGAP HN4                          | squamous cell carcinoma                               | pharynx       | Bluescript SK- |
|       |                                       | epithelium (cell line)                                | prostate      | Bluescript SK- |
| L0383 | NCI CGAP Pr24                         | invasive tumor (cell line)                            | prostate      | Bluescript SK- |
| L0384 | NCI CGAP Pr23                         | prostate tumor                                        | prostate      | Bluescript SK- |
| L0386 | NCI_CGAP_HN3                          | squamous cell carcinoma from<br>base of tongue        | ongnot        | Bluescript SK- |
| L0388 | NCI_CGAP_HN6                          | normal gingiva (cell line from<br>immortalized kerati |               | Bluescript SK- |
| L0411 | 1-NIB                                 |                                                       |               | Lafmid BA      |
| L0415 | b4HB3MA Cot8-HAP-Ft                   |                                                       |               | Lafmid BA      |
| L0435 | -                                     |                                                       |               | lafmid BA      |
|       | Dr. M. Soares INIB                    |                                                       |               |                |
| L0438 | normalized infant brain<br>cDNA       | total brain                                           | brain         | lafmid BA      |
| L0439 | Soares infant brain 1NIB              |                                                       | whole brain   | Lafmid BA      |
| L0454 | L0454   Clontech adult human fat cell |                                                       |               | lambda gt10    |

|        | 131 III 1108 A                                    |                              |             |       |       |                    |
|--------|---------------------------------------------------|------------------------------|-------------|-------|-------|--------------------|
| 20,00  | ilorary nel 106A                                  | ,                            |             |       |       |                    |
| L0455  | Human retina cDNA<br>randomly primed sublibrary   | retina                       | eye         |       | lami  | lambda gt10        |
| L0456  | Human retina cDNA                                 | retina                       | eye         |       | lamk  | lambda gt10        |
| L0463  | fetal brain cDNA                                  | brain                        | brain       |       | lamb  | lambda et11        |
| L0465  | TEST1, Human adult Testis                         |                              |             |       | lamb  | lambda nm1149      |
| L0471  | Human fetal heart, Lambda                         |                              |             |       | Lam   | Lambda ZAP Express |
| L0475  | KG1-a Lambda Zap Express                          |                              |             | KG1-a | Lam   | Lambda Zap Express |
| 20,0   | CLUNA IIDIARY                                     |                              |             |       | anc)  | (Stratagene)       |
| 1.0476 | Stratagene Cat#027717 (1007)                      |                              |             |       | Lam   | Lambda ZAP II      |
| L0481  | CD34+DIRECTIONAL                                  |                              |             |       | Lam   | Lambda ZAPII       |
| L0483  | Human pancreatic islet                            |                              |             |       | Lam   | Lambda ZAPII       |
| L0485  | STRATAGENE Human<br>skeletal muscle cDNA library, | skeletal muscle              | əjəsnın gəj |       | Lam   | Lambda ZAPII       |
| L0492  | Cat. #936213.<br>Human Genomic                    |                              |             |       | MAG   | /Ib                |
| L0493  | NCI CGAP Ov26                                     | papillary scrous carcinoma   | ovary       |       | PAMP  | AP1                |
| L0497  | NCI_CGAP_HSC4                                     | CD34+, CD38- from normal     | bone marrow |       | pAMP1 | AP1                |
| 1.0400 | NCI CGAP HSC2                                     | stem cell 34+/38+            | hone marrow |       | 14MP1 | /bi                |
| L0500  | NCI CGAP Brn20                                    | oligodendroglioma            | brain       |       | pAMP1 | AP1                |
| L0503  | NCI CGAP Br17                                     | adenocarcinoma               | breast      |       | pAMP1 | AP1                |
| 9050T  | NCI_CGAP_Br16                                     | lobullar carcinoma in situ   | breast      |       | pAMP1 | AP1                |
| 60S0T  | NCI_CGAP_Lu26                                     | invasive adenocarcinoma      | gunį        |       | pAMP1 | AP1                |
| L0510  | NCI CGAP Ov33                                     | borderline ovarian carcinoma | ovary       |       | pAMP  | AP1                |
| L0511  | NCI CGAP Ov34                                     | borderline ovarian carcinoma | ovary       |       | pAMP. | AP1                |
| L0514  | NCI_CGAP_Ov31                                     | papillary serous carcinoma   | ovary       |       | pAMP  | AP1                |
| L0515  | NCI_CGAP_Ov32                                     | papillary serous carcinoma   | ovary       |       | pAMP1 | AP1                |
| L0517  | NCI CGAP Pr1                                      |                              |             |       | pAN   | pAMP10             |
| L0518  | NCI_CGAP_Pr2                                      |                              |             |       | pAN   | pAMP10             |
| L0519  | NCI CGAP Pr3                                      |                              |             |       | pAN   | pAMP10             |
| L0520  | L0520 NCI CGAP Alv1                               | alveolar rhabdomyosarcoma    |             |       | pAN   | pAMP10             |

| nAMP10          | pAMP10        | pAMP10        | pAMP10                          | pAMP10       | pAMP10       | pAMP10       | pAMP10       | pAMP10        | pAMP10        | pAMP10                                   | pAMP10                 | pAMP10                  | pAMP10                            | pAMP10                            | pAMP10                                              | pAMP10                                              | pAMP10                 | pAMP10                          | pAMP10                                 | pAMP10                                             | pAMP10                     | pAMP10                            | pBluescript            | pBluescript                           | pBluescript SK             | pBluescript SK(-) |   |
|-----------------|---------------|---------------|---------------------------------|--------------|--------------|--------------|--------------|---------------|---------------|------------------------------------------|------------------------|-------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------------|-----------------------------------------------------|------------------------|---------------------------------|----------------------------------------|----------------------------------------------------|----------------------------|-----------------------------------|------------------------|---------------------------------------|----------------------------|-------------------|---|
|                 |               |               |                                 |              |              |              |              |               |               |                                          |                        |                         |                                   |                                   |                                                     |                                                     |                        |                                 |                                        |                                                    |                            | line;                             |                        |                                       |                            |                   |   |
| ŀ               |               |               |                                 |              |              |              |              |               | W             |                                          |                        |                         |                                   |                                   |                                                     |                                                     |                        |                                 |                                        |                                                    |                            | HeLa cell line;<br>ATCC           |                        |                                       |                            |                   |   |
|                 |               |               |                                 |              |              |              |              |               | bone marrow   | brain                                    | placenta               | prostate                | prostate                          | prostate                          | prostate                                            | prostate                                            | colon                  | ovary                           | ovary                                  | tongue                                             | tongue                     |                                   |                        | Нiр                                   | liver                      |                   |   |
| Fwino"s sarcoma | kidney        | liposarcoma   | metastatic prostate bone lesion | ovary        | prostate     | prostate     | prostate     | thyroid       | stem cells    | brain                                    |                        | invasive prostate tumor | normal prostatic epithelial cells | normal prostatic epithelial cells | prostatic intraepithelial neoplasia<br>- high grade | prostatic intraepithelial neoplasia<br>- high grade | colonic adenocarcinoma | endometrioid ovarian metastasis | papillary serous ovarian<br>metastasis | moderate to poorly differentiated invasive carcino | normal squamous epithelium |                                   | bone marrow stroma     | Bone                                  |                            |                   |   |
| NCI CGAP Fw1    | NCI CGAP Kidl | NCI CGAP Lip2 | NCI CGAP Pr12                   | NCI CGAP Ov2 | NCI CGAP Pr5 | NCI CGAP Pr6 | NCI CGAP Pr8 | NCI CGAP Thy1 | NCI CGAP HSC1 | Chromosome 7 Fetal Brain<br>cDNA Library | Chromosome 7 Placental | NCI CGAP Pr10           | NCI CGAP Pr11                     | NCI CGAP Pr9                      | NCI_CGAP_Pr4                                        | NCI_CGAP_Pr4.1                                      | NCI_CGAP_Co22          | NCI CGAP Ov40                   | NCI_CGAP_Ov39                          | NCI_CGAP_HN12                                      | NCI CGAP HN11              | Chromosome 7 HeLa cDNA<br>Library | Jia bone marrow stroma | Normal Human Trabecular<br>Bone Cells | Stratagene liver (#937224) | HTCDL1            |   |
| T 0521          | -             | L0523         | L0526                           | L0527        |              | L0529        |              | L0532         |               | L0534                                    | L0539                  | L0540                   | L0542                             | L0543                             | L0544                                               | L0545                                               |                        |                                 | 65507                                  | 09507                                              | T950T                      | L0562                             | L0564                  | F0565                                 | L0581                      | Н                 | Г |

|           | 1 037773                                      |                         |                 |         |                              |
|-----------|-----------------------------------------------|-------------------------|-----------------|---------|------------------------------|
| L0589     | Stratagene fetal retina 937202                |                         |                 |         | pBluescript SK-              |
| T0590     | Stratagene fibroblast<br>(#937212)            |                         |                 |         | pBluescript SK-              |
| L0591     | Stratagene HeLa cell s3<br>937216             |                         |                 |         | pBluescript SK-              |
| L0592     | Stratagene hNT neuron<br>(#937233)            |                         |                 |         | pBluescript SK-              |
| L0593     | Stratagene neuroepithelium<br>(#937231)       |                         |                 |         | pBluescript SK-              |
| L0594     | Stratagene neuroepithelium<br>NT2RAMI 937234  |                         |                 |         | pBluescript SK-              |
| F0595     | Stratagene NT2 neuronal<br>precursor 937230   | neuroepithelial cells   | brain           |         | pBluescript SK-              |
| F0596     | Stratagene colon (#937204)                    |                         | colon           |         | pBluescript SK-              |
| F0598     | Morton Fetal Cochlea                          | cochlea                 | ear             |         | pBluescript SK-              |
| F0599     | Stratagene lung (#937210)                     |                         | lung            |         | pBluescript SK-              |
| T0600     | Weizmann Olfactory<br>Epithelium              | olfactory epithelium    | nose            |         | pBluescript SK-              |
| L0601     | Stratagene pancreas<br>(#937208)              |                         | pancreas        |         | pBluescript SK-              |
| L0602     | Pancreatic Islet                              | pancreatic islet        | pancreas        |         | pBluescript SK-              |
| L0603     | Stratagene placenta (#937225)                 |                         | placenta        |         | pBluescript SK-              |
| L0604     | Stratagene muscle 937209                      | muscle                  | skeletal muscle |         | pBluescript SK-              |
| T0605     | Stratagene fetal spleen<br>(#937205)          | fetal spleen            | spleen          |         | pBluescript SK-              |
| F0606     | NCI CGAP Lym5                                 | follicular lymphoma     | lymph node      |         | pBluescript SK-              |
| F0608     | Stratagene lung carcinoma<br>937218           | lung carcinoma          | gunl            | NCI-H69 | pBluescript SK-              |
| L0610     | Schiller glioblastoma<br>multiforme           | glioblastoma multiforme | brain           |         | pBluescript SK- (Stratagene) |
| T190T     | Schiller meningioma                           | meningioma              | brain           |         | pBluescript SK- (Stratagene) |
| L0615     | 22 week old human fetal liver<br>cDNA library |                         |                 |         | pBluescriptII SK(-)          |
| L0617     | Chromosome 22 exon                            |                         |                 |         | pBluescriptIIKS+             |
| L0622 HM1 | HMI                                           |                         |                 | _       | pcDNAII (Invitrogen)         |

| L0623   | HM3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | pectoral muscle (after<br>mastectomy)                 |                     | pcDNAII (Invitrogen) |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------|----------------------|
| L0625   | NCI CGAP AR1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | bulk alveolar tumor                                   |                     | pCMV-SPORT2          |
| L0629   | NCI_CGAP_Mel3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | metastatic melanoma to bowel                          | bowel (skin         | pCMV-SPORT4          |
|         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                       | primary)            |                      |
| L0630   | NCI CGAP CNS1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | substantia nigra                                      | brain               | pCMV-SPORT4          |
| L0632   | NCI CGAP Li5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | hepatic adenoma                                       | liver               | pCMV-SPORT4          |
| L0633   | NCI CGAP Lu6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | small cell carcinoma                                  | Jung                | pCMV-SPORT4          |
| L0634   | NCI CGAP Ov8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | serous adenocarcinoma                                 | ovary               | pCMV-SPORT4          |
| L0635   | L0635 NCI_CGAP_PNSI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | dorsal root ganglion                                  | peripheral nervous  | pCMV-SPORT4          |
| 7 0 / u | 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 100 TO 10 |                                                       | system              | SHOOMS AND SO        |
| L0636   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | four pooled pituitary adenomas                        | brain               | pCMV-SPORT6          |
| L0637   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | three pooled meningiomas                              | brain               | pCMV-SPORT6          |
| L0638   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | tumor, 5 pooled (see description)                     | brain               | pCMV-SPORT6          |
| L0639   | NCI CGAP Bm52                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | tumor, 5 pooled (see description)                     | brain               | pCMV-SPORT6          |
| L0640   | NCI_CGAP_Br18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | four pooled high-grade tumors,                        | breast              | pCMV-SPORT6          |
| L0641   | NCI CGAP Co17                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | invenile granulosa tumor                              | colon               | DCMV-SPORT6          |
| 1.0642  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | moderately differentiated                             | colon               | PCMV-SPORT6          |
| 71007   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adenocarcinoma                                        | TOOLOGI             | <br>point v sa on to |
| L0643   | NCI_CGAP_Co19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | moderately differentiated                             | colon               | pCMV-SPORT6          |
|         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adenocarcinoma                                        |                     |                      |
| L0644   | NCI_CGAP_Co20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | moderately differentiated                             | colon               | pCMV-SPORT6          |
| L0645   | NCI_CGAP_Co21                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | moderately differentiated                             | colon               | pCMV-SPORT6          |
| L0646   | NCI CGAP Co14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | moderately-differentiated                             | colon               | pCMV-SPORT6          |
|         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | adenocarcinoma                                        |                     |                      |
| L0647   | NCI_CGAP_Sar4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | five pooled sarcomas, including<br>myxoid liposarcoma | connective tissue   | pCMV-SPORT6          |
| L0648   | NCI CGAP Eso2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | souamous cell carcinoma                               | esophagus           | pCMV-SPORT6          |
| L0649   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 2 pooled high-grade transitional cell tumors          | genitourinary tract | pCMV-SPORT6          |
| L0650   | L0650 NCI_CGAP_Kid13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 2 pooled Wilms" tumors, one                           | kidney              | pCMV-SPORT6          |
| 1.0651  | L0651 NCI CGAP Kid8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | renal cell tumor                                      | kidnev              | pCMV-SPORT6          |

| pCMV-SPORT6                                       | pCMV-SPORT6                         | pCMV-SPORT6     | pCMV-SPORT6                                        | pCMV-SPORT6       | pCMV-SPORT6                       | pCMV-SPORT6                       | pCMV-SPORT6    | pCMV-SPORT6                                     | pCMV-SPORT6                                           | pCMV-SPORT6               | pCMV-SPORT6           |                             | pCMV-SPORT6                                           | pCMV-SPORT6                                       | pCMV-SPORT6                                        | pCR2.1-TOPO (Invitrogen)       | pCR2.1-TOPO (Invitrogen)       | pCRII              | PGEM 5zf(+) | pOTB7           | pOTB7                | pSPORT1 | pSPORT1  | pT7T3-Pac                        | pT7T3D                        |
|---------------------------------------------------|-------------------------------------|-----------------|----------------------------------------------------|-------------------|-----------------------------------|-----------------------------------|----------------|-------------------------------------------------|-------------------------------------------------------|---------------------------|-----------------------|-----------------------------|-------------------------------------------------------|---------------------------------------------------|----------------------------------------------------|--------------------------------|--------------------------------|--------------------|-------------|-----------------|----------------------|---------|----------|----------------------------------|-------------------------------|
|                                                   |                                     | _               |                                                    |                   |                                   |                                   |                |                                                 |                                                       |                           |                       |                             |                                                       |                                                   |                                                    |                                |                                |                    |             |                 |                      |         |          |                                  |                               |
|                                                   |                                     |                 |                                                    |                   |                                   |                                   |                |                                                 |                                                       |                           |                       |                             |                                                       |                                                   |                                                    |                                |                                |                    |             |                 | MGC3                 |         |          |                                  |                               |
| gunį                                              | Bunį                                | lung, cell line | opou qduuki                                        | ovary             | ovary                             | ovary                             | bancreas       | skin                                            | stomach                                               | uterus                    | uterus                |                             | uterus                                                | sməm                                              | poold slodw                                        | brain                          | brain                          |                    |             | placenta        | Bunj                 |         |          | smojn                            |                               |
| four pooled poorly-differentiated adenocarcinomas | two pooled squamous cell carcinomas |                 | lymphoma, follicular mixed<br>small and large cell | normal epithelium | tumor, 5 pooled (see description) | tumor, 5 pooled (see description) | adenocarcinoma | malignant melanoma, metastatic<br>to lymph node | poorly differentiated<br>adenocarcinoma with signet r | moderately-differentiated | poorly-differentiated | endometrial adenocarcinoma, | serous papillary carcinoma, high<br>grade, 2 pooled t | well-differentiated endometrial adenocarcinoma, 7 | myeloid cells, 18 pooled CML cases, BCR/ABL rearra | frontal lobe (see description) | frontal lobe (see description) |                    |             | choriocarcinoma | small cell carcinoma |         |          |                                  |                               |
| L0652 NCI_CGAP_Lu27                               | L0653 NCI_CGAP_Lu28                 | NCI CGAP Lu31   | L0655 NCI_CGAP_Lym12                               |                   | NCI_CGAP_Ov23                     | NCI CGAP Ov35                     | NCI_CGAP_Pan1  | NCI_CGAP_Mel15                                  | NCI_CGAP_Gas4                                         | NCI_CGAP_Ut2              | NCI_CGAP_Ut3          |                             | NCI_CGAP_Ut4                                          | NCI_CGAP_Uil                                      | NCI_CGAP_CML1                                      | Stanley Frontal NS pool 2      | Stanley Frontal SN pool 2      | Testis, Subtracted | Testis 2    | NIH MGC 21      | NIH_MGC_7            |         | Testis 5 | Soares_pregnant_uterus_NbH<br>PU | L0738 Human colorectal cancer |
| L0652                                             | L0653                               | L0654           | T0655                                              | F0656             | L0657                             | F0658                             | L0659          | T0661                                           | T0662                                                 | F0993                     | L0664                 |                             | T0665                                                 | 9990T                                             | L0667                                              | F890T                          | 9890T                          | T0690              | R690T       | F0709           | L0710                |         | L0718    | L0731                            | L0738                         |

| L0740 | Soares melanocyte 2NbHM                  | melanocyte                 |                   |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
|-------|------------------------------------------|----------------------------|-------------------|--|---------------------------------------------------------|
| L0741 | Soares adult brain<br>N2b4HB55Y          |                            | brain             |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0742 | Soares adult brain<br>N2b5HB55Y          |                            | brain             |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0743 | Soares breast 2NbHBst                    |                            | breast            |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0744 | Soares breast 3NbHBst                    |                            | breast            |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0745 | Soares retina N2b4HR                     | retina                     | eye               |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0746 | Soares retina N2b5HR                     | retina                     | eye               |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0747 | Soares_fetal_heart_NbHH19                |                            | heart             |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0748 | Soares fetal liver spleen<br>INFLS       |                            | Liver and Spleen  |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0749 | Soares_fetal_liver_spleen_IN<br>FLS_SI   |                            | Liver and Spleen  |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0750 | Soares_fetal_lung_NbHL19W                |                            | gunl              |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0751 | Soares ovary tumor NbHOT                 | ovarian tumor              | ovary             |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0752 | Soares_parathyroid_tumor_N<br>bHPA       | parathyroid tumor          | parathyroid gland |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0753 | Soares_pineal_gland_N3HPG                |                            | pineal gland      |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0754 | Soares placenta Nb2HP                    |                            | placenta          |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| L0755 | Soares_placenta_8to9weeks_<br>2NbHP8to9W |                            | placenta          |  | pT7T3D (Pharmacia) with a<br>modified polylinker        |
| T0756 | Soares_multiple_sclerosis_2N<br>bHMSP    | multiple sclerosis lesions |                   |  | pT7T3D (Pharmacia) with a<br>modified polylinker V_TYPE |
| L0757 | Soares_senescent_fibroblasts_<br>NbHSF   | senescent fibroblast       |                   |  | pT7T3D (Pharmacia) with a<br>modified polylinker V TYPE |

| Sanith .            | i) with a                                             | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                            | ı) with a                                |                  | ı) with a                                                                  | a) with a                                                                                                                                   | 1) with a 1) with a 1) with a                                                                                                                                                                                | 1) with a 1) with a 1) with a 1) with a                                                                                                                                                                                                               | i) with a i) with a i) with a i) with a i) with a                                                                                                                                                                                                                                                               |
|---------------------|-------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------|------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10                  | pr./rsb-rac (rnarmacia) with a<br>modified polylinker | pT7T3D-Pac (Pharmacia) with a            | DOIVIDAGE        | modined polylinker<br>pT7T3D-Pac (Pharmacia) with a<br>modified polylinker | modified polyfinker pT7T3D-Pac (Pharmacia) with a modified polyfinker pT7T3D-Pac (Pharmacia) with a modified polyfinker modified polyfinker | modified polyinker prodified polyinker modified polyinker pT/T3D-Pac (Pharmacia) with a modified polyinker pT/T3D-Pac (Pharmacia) with a modified polyinker pT/T3D-Pac (Pharmacia) with a modified polyinker | modified polyimker<br>pTT7312-Pae (Pharmacia) with a<br>modified polylinker<br>pTT7312-Pae (Pharmacia) with a<br>modified polylinker<br>pTT732-Pae (Pharmacia) with a<br>modified polylinker<br>ppTT732-Pae (Pharmacia) with a<br>modified polylinker | mediche polylinker<br>pri7733-Pae (Pharmacia) with a<br>modified polylinker<br>pri7731-Pae (Pharmacia) with a<br>modified polylinker<br>pri7731-Pae (Pharmacia) with a<br>pri7731-Pae (Pharmacia) with a<br>modified polylinker<br>modified polylinker<br>pri7731-Pae (Pharmacia) with a<br>modified polylinker |
| CTOTOT-             | modified                                              | pT7T3D-<br>modified                                  | pT7T3D.<br>modified                                  | pT7T3D.                                              | pT7T3D.<br>modified                                  | pT7T3D-Pac (Pharn<br>modified polylinker |                  | pT7T3D<br>modified                                                         | pT7T3D-<br>modified<br>pT7T3D-<br>modified                                                                                                  | pT7T3D-<br>modified<br>pT7T3D-<br>modified<br>pT7T3D-<br>modified                                                                                                                                            | pT7T3D-<br>modified<br>pT7T3D-<br>pT7T3D-<br>modified<br>pT7T3D-<br>modified<br>modified                                                                                                                                                              | pT773D- modified pT773D- modified pT773D- modified pT773D- pT773D- modified pT773D- modified                                                                                                                                                                                                                    |
|                     |                                                       |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                          |                  |                                                                            |                                                                                                                                             |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                 |
| -                   |                                                       |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                          |                  |                                                                            |                                                                                                                                             |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                 |
|                     |                                                       |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                          |                  |                                                                            |                                                                                                                                             |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                 |
|                     |                                                       |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      |                                                      | brain                                                | brain                                                | colon                                    | colon            |                                                                            | colon                                                                                                                                       | colon                                                                                                                                                                                                        | colon kidney kidney                                                                                                                                                                                                                                   | colon<br>kidney<br>kidney                                                                                                                                                                                                                                                                                       |
|                     |                                                       |                                                      | B-cell, chronic lymphotic<br>leukemia                | breast                                               | breast                                               | colon                                                | germinal center B cell                               | pooled germ cell tumors                              | pooled germ cell tumors                              | anaplastic oligodendroglioma                         | glioblastoma (pooled)                                | adenocarcinoma                           | colon tumor RER+ |                                                                            | colon tumor RER+                                                                                                                            | colon tumor RER+                                                                                                                                                                                             | colon tumor RER+ 2 pooled tumors (clear cell type)                                                                                                                                                                                                    | colon tumor RER+  2 pooled tumors (elear cell type) carcinoid                                                                                                                                                                                                                                                   |
| Comment April MITTE | TO/20 Sogres resus NHI                                | Soares_total_fetus_Nb2HF8_<br>9w                     | NCI_CGAP_CLL1                                        | NCI_CGAP_Br1.1                                       | NCI_CGAP_Br2                                         | NCI_CGAP_Co3                                         | NCI_CGAP_GCB1                                        | NCI_CGAP_GC3                                         | NCI_CGAP_GC4                                         | NCI_CGAP_Bm25                                        | NCI_CGAP_Bm23                                        | NCI_CGAP_Co8                             | NCT CGAP Co10    |                                                                            | NCI_CGAP_Co9                                                                                                                                | NCI_CGAP_Kid3                                                                                                                                                                                                |                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                 |
| 0.57.0.T            | P0/30                                                 | L0759                                                | 19207                                                | L0762                                                | L0763                                                | L0764                                                | F0766                                                | L0767                                                | F0768                                                | F0769                                                | L0770                                                | L0771                                    | L0772            | _                                                                          |                                                                                                                                             |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                 |

| p1/13D-Fac (Fharmacia) with a                        |  | kidney      |                         | NCI_CGAP_NIGIT          | LU8U3  |
|------------------------------------------------------|--|-------------|-------------------------|-------------------------|--------|
| modified polylinker                                  |  |             |                         | $\rightarrow$           | 4000 A |
| pT7T3D-Pac (Pharmacia) with a                        |  | uojoo       | colon tumor, RER+       | NCI_CGAP_Co16           | L0800  |
| modified polylinker                                  |  |             |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  | prain       | medulloblastoma         | NCI_CGAP_Bm50           | P0796  |
| modified polylinker                                  |  |             |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  |             | pooled germ cell tumors | L0794 NCI_CGAP_GC6      | L0794  |
| modified polylinker                                  |  |             |                         | 1                       |        |
| pT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI CGAP Sub7           | L0793  |
| modified polylinker                                  |  |             |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI_CGAP_Sub6           | L0792  |
| modified polylinker                                  |  |             |                         | _                       |        |
| pT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI CGAP Sub5           | L0791  |
| modified polylinker                                  |  |             |                         |                         |        |
| nT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI CGAP Sub4           | 1.0700 |
| pT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI_CGAP_Sub3           | L0789  |
| modified polylinker                                  |  |             |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI_CGAP_Sub2           | L0788  |
| modified polylinker                                  |  |             |                         | 1                       |        |
| pT7T3D-Pac (Pharmacia) with a                        |  |             |                         | NCI CGAP Sub1           | L0787  |
| modified polylinker                                  |  |             |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  | whole brain |                         | Soares NbHFB            | L0786  |
| modified polylinker                                  |  | mands.      |                         |                         | 1      |
| nT7T3D-Pac (Pharmacia) with a                        |  | uoojus      |                         | Barstead spleen HPI BB2 | 1.0785 |
| p1/13D-rac (rnarmacia) wini a<br>modified polylinker |  | ansan nos   | петоппуозагсоппа        | NCI_COMP_Leiz           | F0/07  |
| modified polylinker                                  |  |             |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  | prostate    | normal prostate         | NCI_CGAP_Pr22           | L0783  |
| modified polylinker                                  |  |             |                         | _                       |        |
| pT7T3D-Pac (Pharmacia) with a                        |  | prostate    | normal prostate         | NCI CGAP Pr21           | L0782  |
| modified polylinker                                  |  |             |                         | P SI                    |        |
| pT7T3D-Pac (Pharmacia) with a                        |  | palood      |                         | Soares NSF F8 9W OT PA  | L0780  |
| modified polylinker                                  |  | namad.      |                         |                         |        |
| pT7T3D-Pac (Pharmacia) with a                        |  | pajood      |                         | Soares NFL T GBC S1     | L0779  |

| L0804  | L0804 NCI_CGAP_Kid12 | 2 pooled tumors (clear cell type)                    | kidney    | Id       | pT7T3D-Pac (Pharmacia) with a<br>modified polylinker |
|--------|----------------------|------------------------------------------------------|-----------|----------|------------------------------------------------------|
| F0802  | NCI_CGAP_Lu24        | carcinoid                                            | gunl      | PT<br>m  | pT7T3D-Pac (Pharmacia) with a<br>modified polylinker |
| 7080F  | NCI_CGAP_Lu19        | squamous cell carcinoma, poorly<br>differentiated (4 | gunl      | pT<br>m  | pT7T3D-Pac (Pharmacia) with a<br>modified polylinker |
| L0807  | L0807 NCI_CGAP_Ov18  | fibrotheoma                                          | ovary     | Tq       | pT7T3D-Pac (Pharmacia) with a<br>modified polylinker |
| F0809  | L0809 NCI_CGAP_Pr28  |                                                      | prostate  | Td M     | pT7T3D-Pac (Pharmacia) with a<br>modified polylinker |
| L0811  | BATM2                |                                                      |           | IM       | PTZ18                                                |
| F0879  | BT0254               |                                                      | breast    | nd       | puc18                                                |
| L0946  | BT0333               |                                                      | breast    | nd       | puc18                                                |
| L1441  | CT0249               |                                                      | uoloo     | nd       | puc18                                                |
| L1499  | CT0322               |                                                      | colon     | nd       | puc18                                                |
| L1788  | HT0229               |                                                      | head_neck | nd       | puc18                                                |
| L1877  | HT0340               |                                                      | head_neck | nd       | puc18                                                |
| L1942  | HT0452               |                                                      | head_neck | nd       | puc18                                                |
| L2251  | Human fetal lung     | Fetal lung                                           |           |          |                                                      |
| L2255  | GLC                  | corresponding non cancerous<br>liver tissue          |           | gd       | pBluescript sk(-)                                    |
| L2257  | NIH MGC 65           | adenocarcinoma                                       | colon     | Dd       | pCMV-SPORT6                                          |
| L2258  | NIH MGC 67           | retinoblastoma                                       | eye       | Dd       | pCMV-SPORT6                                          |
| L2259  | NIH MGC 68           | large cell carcinoma                                 | lung      | DC       | pCMV-SPORT6                                          |
| L2260  | NIH_MGC_69           | large cell carcinoma,<br>undifferentiated            | Bunı      | bC       | pCMV-SPORT6                                          |
| L2261  | NIH MGC 70           | epithelioid carcinoma                                | pancreas  | )d       | pCMV-SPORT6                                          |
| L2262  | NIH MGC 72           | melanotic melanoma                                   | skin      | Dd       | pCMV-SPORT6                                          |
| L2263  |                      | adenocarcinoma                                       | ovary     | ) DC     | pCMV-SPORT6                                          |
| L2265  | NIH MGC 39           | adenocarcinoma                                       | pancreas  | ) bC     | pOTB7                                                |
| L2270  |                      | dorsal root ganglia                                  |           | PC<br>Te | pCMV-SPORT6 (Life<br>Technologies)                   |
| L2281  | BT0701               |                                                      | breast    | nd       | puc18                                                |
| L2333  |                      |                                                      | colon     | nd       | puc18                                                |
| L2338  | CT0432               |                                                      | colon     | nd       | puc18                                                |
| T.2346 | L2346 CT0483         |                                                      | uoloo     | 1        | mic18                                                |

| puc18          | puc18          | puc18          | puc18      | puc18     | puc18     | puc18     | puc18     | puc18     | puc18     | puc18     | puc18      | puc18     | puc18     | puc18     | pOTB7              | pDNR-LIB (Clontech) | pOTB7                    | pDNR-LIB (Clontech)                | pDNR-LIB (Clontech)                  | puc18         | puc18         | puc18         | puc18          | puc18          | puc18    | puc18  | puc18  | puc18         | puc18         | puc18         | puc18         | puc18         |
|----------------|----------------|----------------|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|------------|-----------|-----------|-----------|--------------------|---------------------|--------------------------|------------------------------------|--------------------------------------|---------------|---------------|---------------|----------------|----------------|----------|--------|--------|---------------|---------------|---------------|---------------|---------------|
| nervous normal | nervous normal | nervous normal | head_neck  | head neck | head neck | head neck | head neck | head neck | head neck | head_neck | head_neck  | head neck | head neck | head neck | skin               | kidney              | ovary                    | bone marrow                        | bone marrow                          | nervous tumor | nervous tumor | nervous_tumor | prostate tumor | prostate_tumor | uterus   | uterus | uterus | anmion_normal | amnion normal | breast_normal | breast_normal | breast_normal |
|                |                |                |            |           |           |           |           |           |           |           |            |           |           |           | melanotic melanoma | hypernephroma       | adenocarcinoma cell line | from acute myelogenous<br>leukemia | from chronic myelogenous<br>leukemia |               |               |               |                |                |          |        |        |               |               |               |               |               |
| 9 NN1022       |                | 7 NN1112       | 7   HT0408 |           | 1 HT0559  | 5 HT0594  | -         | 2 HT0704  |           | 0 HT0728  | 2   HT0760 | 9 HT0810  |           |           | Т                  | т                   |                          | 5 NIH_MGC_55                       | 7 NIH_MGC_54                         | 1 NT0048      | 2 NT0098      | 6 NT0117      | 4 FT0128       |                | 2 UM0009 | -      |        | 5 AN0004      |               |               |               | 6 BN0047      |
| L2439          | L2440          | L2467          | L2477      | L2490     | L2491     | L2495     | L2504     | L2522     | L2539     | L2540     | L2562      | L2599     | L2634     | L2637     | L2651              | L2653               | L2654                    | L2655                              | L2657                                | L2681         | L2702         | L2716         | L2814          | L2817          | L2842    | L2852  | L2854  | L2865         | L2884         | L2902         | L2905         | L2906         |

| L2918  | BN0114     |                          | breast normal   |   | puc18               |
|--------|------------|--------------------------|-----------------|---|---------------------|
| L2919  | BN0115     |                          | breast normal   |   | puc18               |
| L3002  | BN0276     |                          | breast_normal   |   | puc18               |
| L3058  | EN0004     |                          | lung normal     |   | puc18               |
| L3081  | ET0005     |                          | lung tumor      |   | puc18               |
| L3089  | ET0018     |                          | lung tumor      |   | puc18               |
| L3092  | ET0023     |                          | lung tumor      |   | puc18               |
| L3127  | ET0084     |                          | lung tumor      |   | puc18               |
| L3144  | MT0035     |                          | marrow          |   | puc18               |
| L3154  | MT0050     |                          | marrow          |   | puc18               |
| L3212  | 9400IO     |                          | ovary           |   | puc18               |
| L3255  | FN0064     |                          | prostate normal |   | puc18               |
| L3311  | FN0180     |                          | prostate normal |   | puc18               |
| L3312  | FN0181     |                          | prostate_normal |   | puc18               |
| L3316  | FN0188     |                          | prostate normal |   | puc18               |
| L3327  | SN0024     |                          | stomach normal  |   | puc18               |
| L3330  | SN0041     |                          | stomach_normal  |   | puc18               |
| L3352  | TN0027     |                          | testis normal   |   | puc18               |
| L3374  | TN0070     |                          | testis normal   |   | puc18               |
| L3378  | 0800NL     |                          | testis_normal   |   | puc18               |
| L3388  | GKC        | hepatocellular carcinoma |                 |   | pBluescript sk(-)   |
| L3391  | NIH MGC_53 | carcinoma, cell line     | bladder         |   | pDNR-LIB (Clontech) |
| L3403  | V800NV     |                          | amnion_normal   |   | puc18               |
| L3432  | CT0461     |                          | colon           |   | puc18               |
| L3466  | GN0020     |                          | placenta_normal |   | puc18               |
| L3485  | GN0070     |                          | placenta_normal |   | puc18               |
| L3504  | HT0873     |                          | head_neck       |   | puc18               |
|        | 6280IH     |                          | head_neck       |   | puc18               |
| L3521  | HT0919     |                          | head_neck       |   | puc18               |
| L3530  | HT0939     |                          | head_neck       |   | puc18               |
| L3603  | UM0093     |                          | uterus          |   | puc18               |
| L3612  | UT0011     |                          | uterus tumor    |   | puc18               |
| L3631  | UT0072     |                          | uterus tumor    |   | puc18               |
| L3636  | NIH MGC 73 |                          | brain           |   | pDNR-LIB (Clontech) |
| T.3643 | ADB        | Adrenal oland            |                 | _ | nRhipsprint ele(-)  |

| Adrenal gland<br>adrenal cortico adenoma for     |
|--------------------------------------------------|
| Cusning's syndrome                               |
| Hypothalamus                                     |
| Hypothalamus                                     |
| Hypothalamus                                     |
| pheochromocytoma                                 |
| cord blood                                       |
|                                                  |
|                                                  |
| pituitary                                        |
| pituitary tumor                                  |
| Bone marrow                                      |
| Bone marrow                                      |
| whole embryo, mainly head                        |
| whole embryo, mainly body                        |
|                                                  |
|                                                  |
|                                                  |
|                                                  |
|                                                  |
| ovary, tumor tissue                              |
| placenta                                         |
| placenta                                         |
|                                                  |
| glioblastoma with EGFR<br>amplification          |
| anaplastic oligodendroglioma<br>with 1p/19q loss |
| invasive ductal carcinoma, 3<br>pooled samples   |
|                                                  |

| L4556 | NCI_CGAP_HN13 | squamous cell carcinoma                               | enguot      | l pCi | pCMV-SPORT6                                          |
|-------|---------------|-------------------------------------------------------|-------------|-------|------------------------------------------------------|
| L4669 | NCI CGAP Ov41 | serous papillary tumor                                | ovary       | DCI   | pCMV-SPORT6                                          |
| L4747 | NCI_CGAP_Bm41 | oligodendroglioma                                     | brain       | (Td   | pT7T3D-Pac (Pharmacia) with a<br>modified polylinker |
| T2565 | NCI_CGAP_Bm66 | glioblastoma with probably<br>TP53 mutation and witho | brain       | Dd.   | pCMV-SPORT6                                          |
| T2566 | NCI CGAP Bm70 | anaplastic oligodendroglioma                          | brain       | DCI   | pCMV-SPORT6.ccdb                                     |
| L5569 | NCI CGAP HN17 | normal epithelium                                     | nasopharynx | [Vd]  | pAMP10                                               |
| L5574 | NCI CGAP HN19 | normal epithelium                                     | nasopharynx | [Vd]  | pAMP10                                               |
| L5575 | NCI_CGAP_Bm65 | glioblastoma without EGFR<br>amplification            | brain       | Dd    | pCMV-SPORT6                                          |
| L5622 | NCI CGAP Skn3 |                                                       | skin        | Dd .  | pCMV-SPORT6                                          |
| L5623 | NCI CGAP Skn4 | squamous cell carcinoma                               | skin        | Dd    | pCMV-SPORT6                                          |
|       |               |                                                       |             |       |                                                      |

## Description of Table 5

[0150] Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1B.1, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendeltian Inheritance in Man (Online Mendeltian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL:

www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B.1, column 8, as determined using the Morbid Map database.

Table 5

| OMIM Reference | Description                                                  |
|----------------|--------------------------------------------------------------|
| 101000         | Meningioma, NF2-related, sporadic Schwannoma, sporadic       |
| 101000         | Neurofibromatosis, type 2                                    |
| 101000         | Neurolemmomatosis                                            |
| 101000         | Malignant mesothelioma, sporadic                             |
| 102200         | Somatotrophinoma                                             |
| 102772         | [AMP deaminase deficiency, erythrocytic]                     |
| 103600         | [Dysalbuminemic hyperthyroxinemia]                           |
| 103600         | [Dysalbuminemic hyperzincemia], 194470                       |
| 103600         | Analbuminemia                                                |
| 103850         | Aldolase A deficiency                                        |
| 104150         | [AFP deficiency, congenital]                                 |
| 104150         | [Hereditary persistence of alpha-fetoprotein]                |
| 104500         | Amelogenesis imperfecta-2, hypoplastic local type            |
| 104770         | Amyloidosis, secondary, susceptibility to                    |
| 106100         | Angiocdema, hereditary                                       |
| 106210         | Peters anomaly                                               |
| 106210         | Cataract, congenital, with late-onset corneal dystrophy      |
| 106210         | Foveal hypoplasia, isolated, 136520                          |
| 106210         | Aniridia                                                     |
| 107271         | CD59 deficiency                                              |
| 107300         | Antithrombin III deficiency                                  |
| 107670         | Apolipoprotein A-II deficiency                               |
| 107776         | Colton blood group, 110450                                   |
| 107777         | Diabetes insipidus, nephrogenic, autosomal recessive, 222000 |
| 108725         | Atherosclerosis, susceptibility to                           |
| 109560         | Leukemia/lymphoma, B-cell, 3                                 |
| 110700         | Vivax malaria, susceptibility to                             |
| 112261         | Fibrodysplasia ossificans progressiva                        |
| 114550         | Hepatocellular carcinoma                                     |
| 114835         | Monocyte carboxyesterase deficiency                          |
| 115500         | Acatalasemia                                                 |
| 116800         | Cataract, Marner type                                        |
| 116806         | Colorectal cancer                                            |
| 116860         | Cavernous angiomatous malformations                          |
| 118485         | Polycystic ovary syndrome with hyperandrogenemia             |
| 120070         | Alport syndrome, autosomal recessive, 203780                 |
| 120131         | Alport syndrome, autosomal recessive, 203780                 |
| 120131         | Hematuria, familial benign                                   |
| 120140         | Osteoarthrosis, precocious                                   |
| 120140         | SED congenita                                                |
| 120140         | SMED Strudwick type                                          |

| 120140 | Stickler syndrome, type I                                                    |
|--------|------------------------------------------------------------------------------|
| 120140 | Wagner syndrome, type II                                                     |
| 120140 | Achondrogenesis-hypochondrogenesis, type II                                  |
| 120140 | Kniest dysplasia                                                             |
| 120220 | Bethlem myopathy, 158810                                                     |
| 120240 | Bethlem myopathy, 158810                                                     |
| 120260 | Epiphyseal dysplasia, multiple, type 2, 600204                               |
| 120550 | C1q deficiency, type A                                                       |
| 120570 | C1q deficiency, type B                                                       |
| 120575 | C1q deficiency, type C                                                       |
| 120700 | C3 deficiency                                                                |
| 121050 | Contractural arachnodactyly, congenital                                      |
| 121360 | Myeloid leukemia, acute, M4Eo subtype                                        |
| 123000 | Craniometaphyseal dysplasia                                                  |
| 123580 | Cataract, congenital, autosomal dominant                                     |
| 123620 | Cataract, cerulean, type 2, 601547                                           |
| 123940 | White sponge nevus, 193900                                                   |
| 126060 | Anemia, megaloblastic, due to DHFR deficiency                                |
| 126090 | Hyperphenylalaninemia due to pterin-4a-carbinolamine dehydratase deficiency, |
|        | 264070                                                                       |
| 126337 | Myxoid liposarcoma                                                           |
| 126600 | Dovne honeycomb retinal dystrophy                                            |
| 126600 | Drusen, radial, autosomal dominant                                           |
| 129010 | Neuropathy, congenital hypomyelinating, 1                                    |
| 129900 | EEC syndrome-1                                                               |
| 130500 | Elliptocytosis-1                                                             |
| 131100 | Multiple endocrine neoplasia I                                               |
| 131100 | Prolactinoma, hyperparathyroidism, carcinoid syndrome                        |
| 131100 | Carcinoid tumor of lung                                                      |
| 131210 | Atherosclerosis, susceptibility to                                           |
| 131400 | Eosinophilia, familial                                                       |
| 133171 | [Erythrocytosis, familial], 133100                                           |
| 133200 | Erythrokeratodermia variabilis                                               |
| 133780 | Vitreoretinopathy, exudative, familial                                       |
| 134570 | Factor XIIIA deficiency                                                      |
| 134790 | Hyperferritinemia-cataract syndrome, 600886                                  |
| 135940 | Ichthyosis vulgaris, 146700                                                  |
| 136132 | [Fish-odor syndrome], 602079                                                 |
| 136435 | Ovarian dysgenesis, hypergonadotropic, with normal karyotype, 233300         |
| 136530 | Male infertility, familial                                                   |
| 136836 | Fucosyltransferase-6 deficiency                                              |
| 138030 | [Hyperproglucagonemia]                                                       |
| 138040 | Cortisol resistance                                                          |
| 138079 | Hyperinsulinism, familial, 602485                                            |
| 138079 | MODY, type 2, 125851                                                         |
| 138140 | Glucose transport defect, blood-brain barrier                                |
| 138760 | [Glyoxalase II deficiency]                                                   |
| 138981 | Pulmonary alveolar proteinosis, 265120                                       |
| 139191 | Growth hormone deficient dwarfism                                            |
| 139350 | Epidermolytic hyperkeratosis, 113800                                         |
| 139350 | Keratoderma, palmoplantar, nonepidermolytic                                  |
| 140100 | [Anhaptoglobinemia]                                                          |
| 140100 | [Hypohaptogloginemia]                                                        |
| 141750 | Alpha-thalassemia/mental retardation syndrome, type 1                        |
| 141800 | Methemoglobinemias, alpha-                                                   |
| 141800 | Thalassemias, alpha-                                                         |
| 141800 | Erythremias, alpha-                                                          |
| 171000 | Li yanonina, aipita-                                                         |

| 141800 | Heinz body anemias, alpha-                                                |
|--------|---------------------------------------------------------------------------|
| 141850 | Thalassemia, alpha-                                                       |
| 141850 | Erythrocytosis                                                            |
| 141850 | Heinz body anemia                                                         |
| 141850 | Hemoglobin H disease                                                      |
| 141850 | Hypochromic microcytic anemia                                             |
| 142600 | Hemolytic anemia due to hexokinase deficiency                             |
| 143200 | Wagner syndrome                                                           |
| 143200 | Erosive vitreoretinopathy                                                 |
| 143890 | Hypercholesterolemia, familial                                            |
| 145001 | Hyperparathyroidism-jaw tumor syndrome                                    |
| 145981 | Hypocalciuric hypercalcemia, type II                                      |
| 146760 | [IgG receptor I, phagocytic, familial deficiency of]                      |
| 146790 | Lupus nephritis, susceptibility to                                        |
| 147050 | Atopy                                                                     |
| 147141 | Leukemia, acute lymphoblastic                                             |
| 147670 | Rabson-Mendenhall syndrome                                                |
| 147670 | Diabetes mellitus, insulin-resistant, with acanthosis nigricans           |
| 147670 | Leprechaunism                                                             |
| 147781 | Atopy, susceptibility to                                                  |
| 148040 | Epidermolysis bullosa simplex, Koebner, Dowling-Meara, and Weber-Cockayne |
|        | types, 131900, 131760, 131800                                             |
| 148041 | Pachyonychia congenita, Jadassohn-Lewandowsky type, 167200                |
| 148043 | Meesmann corneal dystrophy, 122100                                        |
| 148070 | Liver disease, susceptibility to, from hepatotoxins or viruses            |
| 148370 | Keratolytic winter erythema                                               |
| 148900 | Klippel-Feil syndrome with larvngeal malformation                         |
| 151385 | Leukemia, acute myeloid                                                   |
| 151390 | Leukemia, acute T-cell                                                    |
| 151410 | Leukemia, chronic myeloid                                                 |
| 151440 | Leukemia, T-cell acute lymphoblastoid                                     |
| 151670 | Hepatic lipase deficiency                                                 |
| 152445 | Vohwinkel syndrome, 124500                                                |
| 152445 | Erythrokeratoderma, progressive symmetric, 602036                         |
| 152780 | Hypogonadism, hypergonadotropic                                           |
| 152780 | Male pseudohermaphroditism due to defective LH                            |
| 153455 | Cutis laxa, recessive, type I, 219100                                     |
| 153700 | Macular dystrophy, vitelliform type                                       |
| 154276 | Malignant hyperthermia susceptibility 3                                   |
| 154545 | Chronic infections, due to opsonin defect                                 |
| 155555 | [Red hair/fair skin]                                                      |
| 155555 | UV-induced skin damage, vulnerability to                                  |
| 156850 | Cataract, congenital, with microphthalmia                                 |
| 159000 | Muscular dystrophy, limb-girdle, type 1A                                  |
| 159001 | Muscular dystrophy, limb-girdle, type 1B                                  |
| 160980 | Carney myxoma-endocrine complex                                           |
| 161015 | Mitochondrial complex I deficiency, 252010                                |
| 164009 | Leukemia, acute promyelocytic, NUMA/RARA type                             |
| 164500 | Spinocerebellar ataxia-7                                                  |
| 164731 | Ovarian carcinoma, 167000                                                 |
| 164920 | Piebaldism                                                                |
| 164920 | Mast cell leukemia                                                        |
| 164920 | Mastocytosis with associated hematologic disorder                         |
| 164953 | Liposarcoma                                                               |
| 165240 | Pallister-Hall syndrome, 146510                                           |
| 165240 | Postaxial polydactyly type A1, 174200                                     |
| 165240 | Greig cephalopolysyndactyly syndrome, 175700                              |
|        | 1 0 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2                                   |

|        | 1                                                                                                                    |   |
|--------|----------------------------------------------------------------------------------------------------------------------|---|
| 168461 | Multiple myeloma, 254250                                                                                             |   |
| 168461 | Parathyroid adenomatosis 1                                                                                           |   |
| 168461 | Centrocytic lymphoma                                                                                                 |   |
| 168468 | Metaphyseal chondrodysplasia, Murk Jansen type, 156400                                                               |   |
| 170650 | Periodontitis, juvenile                                                                                              |   |
| 171860 | Hemolytic anemia due to phosphofructokinase deficiency                                                               |   |
| 172400 | Hemolytic anemia due to glucosephosphate isomerase deficiency                                                        |   |
| 172400 | Hydrops fetalis, one form                                                                                            |   |
| 172471 | Glycogenosis, hepatic, autosomal                                                                                     |   |
| 173610 | Platelet alpha/delta storage pool deficiency                                                                         |   |
| 174000 | Medullary cystic kidney disease, AD                                                                                  |   |
| 174810 | Osteolysis, familial expansile                                                                                       |   |
| 176640 | Creutzfeldt-Jakob disease, 123400                                                                                    |   |
| 176640 | Gerstmann-Straussler disease, 137440                                                                                 |   |
| 176640 | Insomnia, fatal familial                                                                                             |   |
| 176880 | Protein S deficiency                                                                                                 |   |
| 178300 | Ptosis, hereditary congenital, 1                                                                                     |   |
| 178640 | Pulmonary alveolar proteinosis, congenital, 265120                                                                   |   |
| 179095 | Male infertility                                                                                                     |   |
| 179615 | Reticulosis, familial histiocytic, 267700                                                                            |   |
| 179615 | Severe combined immunodeficiency, B cell-negative, 601457                                                            |   |
| 179616 | Severe combined immunodeficiency, B cell-negative, 601457  Severe combined immunodeficiency, B cell-negative, 601457 |   |
| 179755 |                                                                                                                      |   |
|        | Renal cell carcinoma, papillary, 1                                                                                   |   |
| 180104 | Retinitis pigmentosa-9                                                                                               |   |
| 180105 | Retinitis pigmentosa-10                                                                                              |   |
| 180200 | Osteosarcoma, 259500                                                                                                 |   |
| 180200 | Pinealoma with bilateral retinoblastoma                                                                              |   |
| 180200 | Retinoblastoma                                                                                                       |   |
| 180200 | Bladder cancer, 109800                                                                                               |   |
| 180385 | Leukemia, acute T-cell                                                                                               |   |
| 180721 | Retinitis pigmentosa, digenic                                                                                        |   |
| 180840 | Susceptibility to IDDM                                                                                               |   |
| 180901 | Malignant hyperthermia susceptibility 1, 145600                                                                      |   |
| 180901 | Central core disease, 117000                                                                                         |   |
| 181405 | Scapuloperoneal spinal muscular atrophy, New England type                                                            |   |
| 181460 | Schistosoma mansoni, susceptibility/resistance to                                                                    |   |
| 181510 | Schizophrenia                                                                                                        |   |
| 182280 | Small-cell cancer of lung                                                                                            |   |
| 182381 | Renal glucosuria, 253100                                                                                             |   |
| 182860 | Pyropoikilocytosis                                                                                                   |   |
| 182860 | Spherocytosis, recessive                                                                                             |   |
| 182860 | Elliptocytosis-2                                                                                                     |   |
| 186580 | Arthrocutaneouveal granulomatosis                                                                                    |   |
| 188070 | Bleeding disorder due to defective thromboxane A2 receptor                                                           |   |
| 188826 | Sorsby fundus dystrophy, 136900                                                                                      | - |
| 189800 | Preeclampsia/eclampsia                                                                                               |   |
| 190685 | Down syndrome                                                                                                        |   |
| 191092 | Tuberous sclerosis-2                                                                                                 |   |
| 191092 | Cervical carcinoma                                                                                                   |   |
|        |                                                                                                                      |   |
| 191315 | Insensitivity to pain, congenital, with anhidrosis, 256800                                                           |   |
| 192090 | Ovarian carcinoma                                                                                                    |   |
| 192090 | Breast cancer, lobular                                                                                               |   |
| 192090 | Endometrial carcinoma                                                                                                |   |
| 192090 | Gastric cancer, familial, 137215                                                                                     |   |
| 192974 | Neonatal alloimmune thrombocytopenia                                                                                 |   |
| 192974 | Glycoprotein la deficiency                                                                                           |   |

| 193235 | Vitreoretinopathy, neovascular inflammatory                                 |
|--------|-----------------------------------------------------------------------------|
| 193300 | Renal cell carcinoma                                                        |
| 193300 | von Hippel-Lindau syndrome                                                  |
| 194070 | Wilms tumor, type 1                                                         |
| 194070 | Denys-Drash syndrome                                                        |
| 194070 | Frasier syndrome, 136680                                                    |
| 203740 | Alpha-ketoglutarate dehydrogenase deficiency                                |
| 205900 | Anemia, Diamond-Blackfan                                                    |
| 208400 | Aspartylglucosaminuria                                                      |
| 209901 | Bardet-Biedl syndrome 1                                                     |
| 212138 | Carnitine-acylearnitine translocase deficiency                              |
| 216550 | Cohen syndrome                                                              |
| 216900 | Achromatopsia                                                               |
| 217800 | Macular corneal dystrophy                                                   |
| 218030 | Apparent mineralocorticoid excess, hypertension due to                      |
| 219800 | Cystinosis, nephropathic                                                    |
| 221770 | Polycystic lipomembranous ostcodysplasia with sclerosing leukencephalopathy |
| 222745 | DECR deficiency                                                             |
| 222800 | Hemolytic anemia due to bisphosphoglycerate mutase deficiency               |
| 222900 | Sucrose intolerance                                                         |
| 227646 | Fanconi anemia, type D                                                      |
| 227650 | Fanconi anemia, type A                                                      |
| 230800 | Gaucher disease                                                             |
| 230800 | Gaucher disease  Gaucher disease with cardiovascular calcification          |
| 231550 | Achalasia-addisonianism-alacrimia syndrome                                  |
| 231670 | Glutaricaciduria, type I                                                    |
| 231675 |                                                                             |
|        | Glutaricaciduria, type IIC                                                  |
| 231680 | Glutaricaciduria, type IIA                                                  |
| 232500 | Glycogen storage disease IV                                                 |
| 232600 | McArdle disease                                                             |
| 233700 | Chronic granulomatous disease due to deficiency of NCF-1                    |
| 236100 | Holoprosencephaly-1                                                         |
| 236200 | Homocystinuria, B6-responsive and nonresponsive types                       |
| 236700 | McKusick-Kaufman syndrome                                                   |
| 240300 | Autoimmune polyglandular disease, type I                                    |
| 245349 | Lacticacidemia due to PDX1 deficiency                                       |
| 245900 | Norum disease                                                               |
| 245900 | Fish-eye disease                                                            |
| 248600 | Maple syrup urine disease, type Ia                                          |
| 249100 | Familial Mediterranean fever                                                |
| 250850 | Hypermethioninemia, persistent, autosomal dominant, due to methionine       |
|        | adenosyltransferase I/III deficiency                                        |
| 253000 | Mucopolysaccharidosis IVA                                                   |
| 253200 | Maroteaux-Lamy syndrome, several forms                                      |
| 259700 | Osteopetrosis, recessive                                                    |
| 259770 | Osteoporosis-pseudoglioma syndrome                                          |
| 259900 | Hyperoxaluria, primary, type 1                                              |
| 261670 | Myopathy due to phosphoglycerate mutase deficiency                          |
| 266200 | Anemia, hemolytic, due to PK deficiency                                     |
| 266600 | Inflammatory bowel disease-l                                                |
| 267750 | Knobloch syndrome                                                           |
| 268800 | Sandhoff disease, infantile, juvenile, and adult forms                      |
| 268800 | Spinal muscular atrophy, HEXB-related                                       |
| 272800 | Tay-Sachs disease                                                           |
| 272800 | [Hex A pseudodeficiency]                                                    |
| 272800 | GM2-gangliosidosis, juvenile, adult                                         |
| 274180 | Thromboxane synthase deficiency                                             |
| 2.7100 | I amount of the control of                                                  |

| 276600 | Tyrosinemia, type II                                                             |
|--------|----------------------------------------------------------------------------------|
| 276700 | Tyrosinemia, type I                                                              |
| 300011 | Menkes disease, 309400                                                           |
| 300011 | Occipital horn syndrome, 304150                                                  |
| 300011 | Cutis laxa, neonatal                                                             |
| 300011 | Mental retardation, X-linked 23, nonspecific                                     |
|        |                                                                                  |
| 300047 | Mental retardation, X-linked 20                                                  |
| 300067 | Subcortical laminar heterotopia, X-linked dominant                               |
| 300067 | Lissencephaly, X-linked                                                          |
| 300071 | Night blindness, congenital stationary, type 2                                   |
| 300075 | Coffin-Lowry syndrome, 303600                                                    |
| 300077 | Mental retardation, X-linked 29                                                  |
| 300110 | Night blindness, congenital stationary, X-linked incomplete, 300071              |
| 300121 | Subcortical laminal heteropia, X-linked, 300067                                  |
| 300121 | Lissencephaly, X-linked, 300067                                                  |
| 300127 | Mental retardation, X-linked, 60                                                 |
| 300600 | Ocular albinism, Forsius-Eriksson type                                           |
| 301000 | Thrombocytopenia, X-linked, 313900                                               |
| 301000 | Wiskott-Aldrich syndrome                                                         |
| 301200 | Amelogenesis imperfecta                                                          |
| 301201 | Amelogenesis imperfecta-3, hypoplastic type                                      |
| 301830 | Arthrogryposis, X-linked (spinal muscular atrophy, infantile, X-linked)          |
| 301835 | Arts syndrome                                                                    |
| 302350 | Nance-Horan syndrome                                                             |
| 302801 | Charcot-Marie-Tooth neuropathy, X-linked-2, recessive                            |
| 305435 | Heterocellular hereditary persistence of fetal hemoglobin, Swiss type            |
| 305450 | FG syndrome                                                                      |
| 306000 | Glycogenosis, X-linked hepatic, type I                                           |
| 306000 | Glycogenosis, X-linked hepatic, type II                                          |
| 307800 | Hypophosphatemia, hereditary                                                     |
| 308800 | Keratosis follicularis spinulosa decalvans                                       |
| 309470 | Mental retardation, X-linked, syndromic-3, with spastic diplegia                 |
| 309500 | Renpenning syndrome-1                                                            |
| 309510 | Mental retardation, X-linked, syndromic-1, with dystonic movements, ataxia, and  |
| 303210 | seizures                                                                         |
| 309605 | Mental retardation, X-linked, syndromic-4, with congenital contractures and low  |
| 303003 | fingertip arches                                                                 |
| 309610 | Mental retardation, X-linked, syndromic-2, with dysmorphism and cerebral atrophy |
| 309850 | Brunner syndrome                                                                 |
| 311050 | Optic atrophy, X-linked                                                          |
| 311200 | Oral-facial-digital syndrome 1                                                   |
| 311850 | Phosphoribosyl pyrophosphate synthetase-related gout                             |
| 312040 | N syndrome, 310465                                                               |
| 312060 | Properdin deficiency, X-linked                                                   |
| 312170 | Pyruvate dehydrogenase deficiency                                                |
| 312170 |                                                                                  |
|        | Retinoschisis                                                                    |
| 313400 | Spondyloepiphyseal dysplasia tarda                                               |
| 313700 | Perineal hypospadias                                                             |
| 313700 | Prostate cancer                                                                  |
| 313700 | Spinal and bulbar muscular atrophy of Kennedy, 313200                            |
| 313700 | Breast cancer, male, with Reifenstein syndrome                                   |
| 313700 | Androgen insensitivity, several forms                                            |
| 314580 | Wieacker-Wolff syndrome                                                          |
| 600040 | Colorectal cancer                                                                |
| 600045 | Xeroderma pigmentosum, group E, subtype 2                                        |
| 600065 | Leukocyte adhesion deficiency, 116920                                            |
| 600079 | Colon cancer                                                                     |
|        |                                                                                  |

| 600140 | D. 1 ( 'T. 1' 100040                                                            |
|--------|---------------------------------------------------------------------------------|
| 600140 | Rubenstein-Taybi syndrome, 180849                                               |
| 600151 | Bardet-Biedl syndrome 3 Long OT syndrome-3                                      |
|        |                                                                                 |
| 600194 | Ichthyosis bullosa of Siemens, 146800                                           |
|        | Spinocerebellar ataxia-4                                                        |
| 600231 | Palmoplantar keratoderma, Bothnia type                                          |
| 600234 | HMG-CoA synthease-2 deficiency                                                  |
| 600273 | Polycystic kidney disease, infantile severe, with tuberous sclerosis            |
| 600276 | Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy, 125310 |
| 600319 | Diabetes mellitus, insulin-dependent, 4                                         |
| 600354 | Spinal muscular atrophy-1, 253300                                               |
| 600354 | Spinal muscular atrophy-2, 253550                                               |
| 600354 | Spinal muscular atrophy-3, 253400                                               |
| 600374 | Bardet-Biedl syndrome 4                                                         |
| 600528 | CPT deficiency, hepatic, type I, 255120                                         |
| 600536 | Myopathy, congenital                                                            |
| 600631 | Enuresis, nocturnal, 1                                                          |
| 600652 | Deafness, autosomal dominant 4                                                  |
| 600678 | Cancer susceptibility                                                           |
| 600757 | Orofacial cleft-3                                                               |
| 600760 | Pseudohypoaldosteronism, type I, 264350                                         |
| 600760 | Liddle syndrome, 177200                                                         |
| 600761 | Pseudohypoaldosteronism, type I, 264350                                         |
| 600761 | Liddle syndrome, 177200                                                         |
| 600795 | Dementia, familial, nonspecific                                                 |
| 600807 | Bronchial asthma                                                                |
| 600808 | Enuresis, nocturnal, 2                                                          |
| 600850 | Schizophrenia disorder-4                                                        |
| 600882 | Charcot-Marie-Tooth neuropathy-2B                                               |
| 600887 | Endometrial carcinoma                                                           |
| 600897 | Cataract, zonular pulverulent-1, 116200                                         |
| 600900 | Muscular dystrophy, limb-girdle, type 2E                                        |
| 600918 | Cvstinuria, type III                                                            |
| 600956 | Persistent Mullerian duct syndrome, type II, 261550                             |
| 600957 | Persistent Mullerian duct syndrome, type I, 261550                              |
| 600975 | Glaucoma 3, primary infantile, B                                                |
| 601072 | Deafness, autosomal recessive 8                                                 |
| 601090 | Iridogoniodysgenesis, 601631                                                    |
| 601105 | Pycnodysostosis, 265800                                                         |
| 601145 | Epilepsy, progressive myoclonic 1, 254800                                       |
| 601238 | Cerebellar ataxia, Cayman type                                                  |
| 601284 | Hereditary hemorrhagic telangiectasia-2, 600376                                 |
| 601313 | Polycystic kidney disease, adult type I, 173900                                 |
| 601362 | DiGeorge syndrome/velocardiofacial syndrome complex-2                           |
| 601386 | Deafness, autosomal recessive 12                                                |
| 601412 |                                                                                 |
|        | Deafness, autosomal dominant 7                                                  |
| 601472 | Charcot-Marie-Tooth neuropathy-2D                                               |
| 601493 | Cardiomyopathy, dilated IC                                                      |
| 601567 | Combined factor V and VIII deficiency, 227300                                   |
| 601596 | Charcot-Marie-Tooth neuropathy, demyelinating                                   |
| 601649 | Blepharophimosis, epicanthus inversus, and ptosis, type 2                       |
| 601650 | Paraganglioma, familial nonchromaffin, 2                                        |
| 601652 | Glaucoma 1A, primary open angle, juvenile-onset, 137750                         |
| 601669 | Hirschsprung disease, one form                                                  |
| 601692 | Reis-Bucklers corneal dystrophy                                                 |
| 601692 | Corneal dystrophy, Avellino type                                                |

| 601692 | Corneal dystrophy, Groenouw type I, 121900                         |
|--------|--------------------------------------------------------------------|
| 601692 | Corneal dystrophy, lattice type I, 122200                          |
| 601769 | Osteoporosis, involutional                                         |
| 601769 | Rickets, vitamin D-resistant, 277440                               |
| 601780 | Ceroid-lipofuscinosis, neuronal-6, variant late infantile          |
| 601785 | Carbohydrate-deficient glycoprotein syndrome, type I, 212065       |
| 601843 | Hypothyroidism, congenital, 274400                                 |
| 601846 | Muscular dystrophy with rimmed vacuoles                            |
| 601863 | Bare lymphocyte syndrome, complementation group C                  |
| 601884 | [High bone mass]                                                   |
| 601920 | Alagille syndrome, 118450                                          |
| 601928 | Monilethrix, 158000                                                |
| 602028 | Multiple myeloma                                                   |
| 602078 | Fibrosis of extraocular muscles, congenital, 2                     |
| 602080 | Paget disease of bone-2                                            |
| 602089 | Hemangioma, capillary, hereditary                                  |
| 602092 | Deafness, autosomal recessive 18                                   |
| 602094 | Lipodystrophy, familial partial                                    |
| 602116 | Glioma                                                             |
| 602121 | Deafness, autosomal dominant nonsyndromic sensorineural, 1, 124900 |
| 602136 | Refsum disease, infantile, 266510                                  |
| 602136 | Zellweger syndrome-1, 214100                                       |
| 602136 | Adrenoleukodystrophy, neonatal, 202370                             |
| 602153 | Monilethrix, 158000                                                |
| 602216 | Peutz-Jeghers syndrome, 175200                                     |
| 602447 | Coronary artery disease, susceptibility to                         |
| 602460 | Deafness, autosomal dominant 15, 602459                            |
| 602477 | Febrile convulsions, familial, 2                                   |
| 602491 | Hyperlipidemia, familial combined, 1                               |
| 602568 | Homocystinuria-megaloblastic anemia, cbl E type, 236270            |
| 602716 | Nephrosis-1, congenital, Finnish type, 256300                      |
| 602783 | Spastic paraplegia-7                                               |

## Mature Polypeptides

[0151] The present invention also encompasses mature forms of a polypeptide having the amino acid sequence of SEO ID NO:Y and/or the amino acid sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEO ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional activities of the full-length or mature form of the polypeptide (e.g., biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the

polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0152] According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretary leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the protein.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.)

However, the two methods do not always produce the same predicted cleavage points) for a given protein. In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table IA.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the predicted mature form of the polypeptide as delineated in columns 14 and 15 of Table 1A. Moreover, fragments or variants of these polypeptides as delineated in columns 14 and 15 of Table 1A. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polymcleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional activities of the full-length or mature form of the polypeptide (e.g., biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention. Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0156] Polynucleotides encoding proteins comprising, or consisting of, the predicted mature form of polypeptides of the invention (e.g., polynucleotides having the sequence of SEQ ID NO: X (Table 1A, column 4), the sequence delineated in columns 7 and 8 of Table 1A, and a sequence encoding the mature polypeptide delineated in columns 14 and 15 of Table 1A (e.g., the sequence of SEQ ID NO:X encoding the mature polypeptide delineated in columns 14 and 15 of Table 1)) are also encompassed by the invention, as are fragments or variants of these polynucleotides (such as, fragments as described herein, polynucleotides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polynucleotides, and nucleic acids which hybridizes under stringent conditions to the complementary strand of the polynucleotide).

[0157] As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO.Y which have an N-terminus beginning within 15 residues of the predicted cleavage point (i.e., having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 more or less contiguous residues of SEQ ID NO.Y at the N-terminus when compared to the predicted mature form of the polypeptide (e.g., the mature polypeptide delineated in columns 14 and 15 of Table 1). Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polypucides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as desribed below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

## Polynucleotide and Polypeptide Variants

In 159] The present invention is also directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:X, the mucleotide sequence of SEQ ID NO:X that encodes the polypeptide sequence as defined in columns 13 and 14 of Table 1A, nucleotide sequences encoding the polypeptide sequence as defined in columns 13 and 14 of Table 1B, nucleotide sequences of SEQ ID NO:X encoding the polypeptide sequence as defined in Table 1B, nucleotide sequences conding the polypeptide sequence as defined in Table 1B, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1C, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1C, the cDNA sequence contained in ATCCT<sup>M</sup> Deposit No:Z, nucleotide sequences encoding the polypeptide encoded by the DPAS sequence contained in ATCCT<sup>M</sup> Deposit No:Z, nucleotide sequences encoding at mature (secreted) polypeptide encoded by the cDNA sequence contained in ATCCT<sup>M</sup> Deposit No:Z, nucleotide in ATCCT<sup>M</sup> Deposit No:Z.

[10160] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, the polypeptide as defined in columns 13 and 14 of Table 1A, the polypeptide sequence as defined in Table 1B, a polypeptide sequence encoded by the polymucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a

polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1C, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO.X., the polypeptide sequence encoded by the cDNA sequence contained in ATCC™ Deposit No.Z and/or a mature (secreted) polypeptide encoded by the cDNA sequence contained in ATCC™ Deposit No.Z.

[0161] "Variant" refers to a polymucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

101621 Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of ATCC™ Deposit No:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in ATCCTM Deposit No:Z which encodes the complete amino acid sequence of SEO ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCCTM Deposit No; Z; (c) a nucleotide sequence in SEO ID NO; X or the cDNA in ATCCTM Deposit No: Z which encodes a mature polypeptide (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)); (d) a nucleotide sequence in SEO ID NO:X or the cDNA sequence of ATCC™ Deposit No:Z, which encodes a biologically active fragment of a polypeptide; (e) a nucleotide sequence in SEO ID NO;X or the cDNA sequence of ATCCTM Deposit No;Z, which encodes an antigenic fragment of a polypeptide; (f) a nucleotide sequence encoding a polypeptide comprising the complete amino acid sequence of SEQ ID NO: Y or the complete amino acid sequence encoded by the cDNA in ATCCTM Deposit No:Z; (g) a nucleotide sequence encoding a mature polypeptide of the amino acid sequence of SEO ID NO:Y (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)) or a mature polypeptide of the amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z: (h) a nucleotide sequence encoding a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z; (i) a nucleotide sequence encoding an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z; and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above.

Intel The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 95%, 96%, 97%, 98%, 99% or 100%, the nucleotide sequences in (a), (b), (c), (d), (d), (f), (f), (g), (f), (f), (f) or (f) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in ATCCT\*\* Deposit No:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in ATCCT\*\* Deposit No:Z, the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide in polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as

defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table IC or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table IC or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in Table IB or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in Table IB or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in Table IB or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[0164] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridization to the complement of these nucleic acid molecules under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of; (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z; (b) the amino acid sequence of a mature (secreted) form of a polypeptide having the amino acid sequence of SEQ ID NO:Y (e.g., as delineated in columns 14 and 15 of Table 1A) or a mature form of the amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z mature; (c) the amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z; and (d) the amino acid sequence of an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z. and (d) the amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC™ Deposit No:Z.

[0166] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 97%, 98%, 99%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in ATCC™ Deposit No:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in Table 1B, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the outleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid

sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a [0167] reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1B or 2 as the ORF (open reading frame), or any fragment specified as described herein. 101681 As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci, 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0. Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

10169] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[0170] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB

program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5° or 3° of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5° and 3° of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

10171] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0172] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., the amino acid sequence delineated in columns 14 and 15) or a fragment thereof, Table 1B.1 (e.g., the amino acid sequence identified in column 6) or a fragment thereof, Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polypucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence of the polypeptide encoded by cDNA contained in ATCCTM Deposit No:Z, or a fragment thereof, the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in ATCCTM Deposit No:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0173] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global

percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

[10174] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to matched/aligned with the purposes of the present invention.

10.175] The polynucleotide variants of the invention may contain alterations in the coding regions, noncoding regions, or both. Especially preferred are polynucleotide variants containing alterations which
produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the
encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the
genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30,
less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in
any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to
optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a
bacterial host such as E. coil).

[0176] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polyopeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by multaenessis techniques or by direct synthesis.

[0177] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (J. Biol. Chem. 268: 2984-2988 (1993)) reported variant KGF proteins having heparin binding activity even after deletting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deletting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0179] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polymentide results in modification or loss of one or more biological functions, other biological activities.

putyper Futnermore, even it detering one or more anino actos from the N-terminis or C-terminis or a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenia extivities can readily be determined by routine methods described herein and otherwise known in the art.

[0180] Thus, the invention further includes polypeptide variants which show a biological or functional activity of the polypeptides of the invention (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus). Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

Intell The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues), and (4) in situ hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues).

[0182] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact,

encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein and/or a mature (secreted) protein of the invention. Such functional activities include, but are not limited to, biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[0183] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[0184] For example, in one embodiment where one is assaying for the ability to bind or compete with a full-length polypeptide of the present invention for binding to an anti-polypetide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blost, precipitation reactions, agglutination assays (e.g., gel agglutination assays, memunodium assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0188] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity bottoms. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[0186] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

[0187] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in ATCC™ Deposit No.Z, the nucleic acid sequence referred to in Table IB (SEQ ID NO.X), the nucleic acid sequence delineated in

columns 7 and 8), the nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[0188] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0189] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0190] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[0191] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the amonatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr. Met. and Gly.

[0192] Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fe fusion region peptide, serum albumin (preferably human serum albumin) or a fragment thereof, or

leader or secretory sequence, or a sequence facilitating purification, or (v) fusion of the polypeptide with another compound, such as albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0193] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

noted A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which, for example, comprises the amino acid sequence of a polypeptide of SEQ ID NO.Y, the amino acid sequence encoded by SEQ ID NO.X, an amino acid sequence encoded by the portion of SEQ ID NO.X as defined in columns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO.X, an amino acid sequence encoded by the complement of SEQ ID NO.X, an amino acid sequence encoded by cDNA contained in ATCC™ Deposit No.Z, and/or the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in ATCC™ Deposit No.Z, or a fragment thereof, which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature formand/or other fragments described herein); (b) the amino acid sequence encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in ATCCT<sup>TM</sup> Deposit No:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polymucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotide and Polyneptide Fragments

[0196] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in ATCC™ Deposit No:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in ATCCTM Deposit No:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the mature (secreted) polypeptide encoded by the cDNA contained in ATCC™ Deposit No:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the mature amino acid sequence as defined in columns 14 and 15 of Table 1A or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEO ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEO ID NO;X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEO ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto. The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in ATCC™ Deposit No:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length ) are also encompassed by the invention.

| Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1360, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4500, 5011-550, 5501-5500, 5501-5500, 5601-5650, 5661-5700, 5701-5750, 5751-5300, 5351-5400, 5611-5600, 5661-5600, 5661-56700, 5701-5750, 5751-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751-5700, 5701-5750, 5751

\$800, \$801-\$850, \$851-\$900, \$901-\$950, \$951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity; such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[01991 Further representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in ATCC™ Deposit No:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polyneptides encoded by these polynucleotides.

[0200] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1C column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1C. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polyneptides are also encompassed by the invention.

[0201] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0202] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C which correspond to the same ATCCTM Deposit No.Z (see Table 1C, column 1), and the polynucleotide sequence of SEQ ID NO.X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

10203] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

10 additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3° 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5° 10 polynucleotides of the sequence of SEQ ID NO;X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polymedeotides and/or nucleic acids, other polymedeotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polymedeotides, nucleic acids, and polypeptides are also encompassed by the invention.

[10205] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3 '10 polynucleotides of one of the sequence of SEQ IID no. (C. e.g., as described herein) are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

10206] In further specific embodiments, polymucleotides of the invention comprise, or alternatively consist of a polymucleotide sequence in which the 3<sup>3</sup> 10 polymucleotides of a fragment or variant of the sequence of SEQ ID NO.X and the 5<sup>3</sup> 10 polymucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polymucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polymucleotides and/or nucleic acids, other polymucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polymucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

no specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3° 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5° 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3° 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5° 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, encoding these polypeptides and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polypucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

10208] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of the amino acid sequence contained in SEQ ID NO.Y, as a portion of the mature form of SEQ ID NO.Y as defined in columns 14 and 15 of Table 1A, a portion of an amino acid sequence encoded by the portion of SEQ ID NO.X as defined in columns 8 and 9 of Table 2, is a portion of an amino acid sequence

encoded by the polynucleotide sequence of SEO ID NO:X, is a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEO ID NO:X, is a portion of the amino acid sequence of a mature (secreted) polypeptide encoded by the cDNA contained in ATCC™ Deposit No;Z, and/or is a portion of an amino acid sequence encoded by the cDNA contained in ATCCTM Deposit No: Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of cDNA and SEQ ID NO: Y. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760. 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEO ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polyneptide fragments are also encompassed by the invention.

10209] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities; such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; ability to multimerize; ability to bind a ligand; antigencia ability useful for production of polypeptides specific antibodies) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain sone biological or

immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

10210] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

102111 The present invention further provides polypeptide having one or more residues deleted from the amino acid sequence of a polypeptide disolsed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polypundeotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the cDNA contained in ATCC™ Deposit No:Z, and/or a mature polypeptide encoded by the cDNA contained in ATCC™ Deposit No:Z, and/or a mature polypeptide encoded by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polymedeotides encoding these polypeptides are also encompassed by the invention.

no212] The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y, as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polymerleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in columns 6 of Table 1C, a polypeptide encoded by the cDNA contained in ATCC™ Deposit No:Z, and/or a mature polypeptide encoded by the cDNA contained in ATCC™ Deposit No:Z, and/or a mature polypeptide encoded by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polymerleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, and the polypeptide encoded by the portion of SEO ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in ATCC™ Deposit No:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polyneptides are also encompassed by the invention.

10214] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminals. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

10215] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polymucleotides encoding these polypeptides are also encompassed by the invention. 10216] Any polypeptide sequence encoded by, for example, the polymucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in ATCCT<sup>TM</sup> Deposit No:Z, or the polymucleotide sequence as defined in column 6 of Table 1C, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polymucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in ATCCT<sup>TM</sup> Deposit No:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; www.dnastar.com)

[0217] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Eimini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above. [0218]

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the

default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

portion of polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antiencificity, immunogenicity, and/or multimerization, as described herein.

10220] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0221] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Epitopes and Antibodies

102221 The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEO ID NO:Y; a polypeptide sequence encoded by SEO ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C or the complement thereto; the polypeptide sequence encoded by the cDNA contained in ATCC™ Deposit No:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEO ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in ATCCTM Deposit No:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined supra. 102231 The term "epitones," as used herein, refers to portions of a polypertide having antigenic or

102231 the term "epitopes," as used herein, reters to portions of a polypeptide naving antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0224] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4.631.211.)

10225] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 7, more preferably at least 8, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 30, at least 10, at least 10, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunossays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

10226] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO.Y specified in Table IB. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNAStar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO.Y shown in Table IB, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO.Y. The flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO.Y. Shown in Table IB.

[0227] Similarly, immunogenic cpitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein,

such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0228] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-pentide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0229] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5.876.969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 - 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0.322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein

(e.g., immunoglobulin Fe polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins as those described above may facilitate purification and may increase half-[0230] life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972-897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazolecontaining buffers.

## Fusion Proteins

10231] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[0232] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[0233] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

10.244 Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the bost cell or subsequent handling and storage. Also, pertide moieties may be added to the

polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[0235] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the polypeptides of the present invention can be fitsed to marker sequences, such as a polypeptide which facilitates purification of the fitsed polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)).

10237] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. Sec. generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to

generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0238] Thus, any of these above fusions can be engineered using the polynucleotides or the polynentides of the present invention.

## Recombinant and Synthetic Production of Polypeptides of the Invention

10.239 The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

10240] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

10241] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tae promoters the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0242] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (c.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC™ Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptern Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art

Mong vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16A, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptre99a, pKK223-3, pKK233-3, pDR540, pFIT available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pCG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia Preferred

expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEFI/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled arrisan

10244] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expression gells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WOS7/04462; WOS8/05807; WOS9/01036; WOS9/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NII). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., Bio/technology 10:169(1992) and in Biblia and Robinson Biotechnol. Prog. 11:1 (1995) which are herein incorporated by reference.

In the present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipidmediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0248] Polypeptides of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant etchniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0250] In one embodiment, the yeast Pichia pastoris is used to express polypeptides of the invention in a cukaryotic system. Pichia pastoris is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, Pichia pastoris must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (AOXI) is highly active. In the presence of methanol, alcohol oxidase produced from the AOXI gene comprises up to approximately 30% of the total soluble protein in Pichia pastoris. See Ellis, S.B., et al., Mol. Cell. Biol. 5:1111-21 (1985); Koutz, P.J. et al., Yeast 5:167-77 (1989); Tschopp, J.F., et al., Nucl. Acids Res., 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the AOXI regulatory sequence is expressed at exceptionally high levels in Pichia yeast grown in the presence of methanol.

[0251] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a Pichea yeast system essentially as described in "Pichia Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong AOX1 promoter linked to the Pichia pastoris alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located unstream of a multiple cloning site.

[0252] Many other yeast vectors could be used in place of pPICOK, such as, pYES2, pVD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPICO, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0253] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5.641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

pio255] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acids analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 24-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, a-composition acids, and a continuous caid, Abi, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino bexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cystcic acid, t-butylglycine, t-butylalamine, phenylglycine, cyclohexylalamine, b-alamine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0256] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule

or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of funicamycin; etc.

[0257] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical motifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

10289 Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, betagalactosidase, or acctylcholinesterase; examples of suitable prosthetic group complexes include
streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone,
fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or
phycocrythrin; an example of a luminescent material includes luminol; examples of bioluminescent
materials include luciferase, luciferin, and acquorin; and examples of suitable radioactive material include
iodine (2<sup>13</sup>L, <sup>123</sup>L, <sup>131</sup>L, <sup>131</sup>L), carbon (4<sup>1</sup>C), sulfur (8<sup>8</sup>S), trittum (4<sup>8</sup>H), indium (1<sup>11</sup>In, 1<sup>12</sup>In, 1<sup>138</sup>In, 1<sup>138</sup>In, 1<sup>138</sup>In),
technetium (8<sup>8</sup>Te, <sup>588</sup>Te), thallium (8<sup>3</sup>Ti), gallium (8<sup>8</sup>Ga, 5<sup>7</sup>Ga), palladium (1<sup>10</sup>Pd), molybedenum (8<sup>8</sup>Mo),
xenon (1<sup>33</sup>Xe), fluorine (1<sup>8</sup>F), 1<sup>33</sup>Sm, 1<sup>77</sup>Lu, 1<sup>139</sup>Gd, 1<sup>39</sup>Pm, 1<sup>40</sup>La, 1<sup>73</sup>Yb, 1<sup>56</sup>Ho, \*Y, \*7<sup>8</sup>Sc, 1<sup>56</sup>Re, \*1<sup>88</sup>Re, 1<sup>42</sup>Pr,
1<sup>55</sup>Rh, and \*<sup>97</sup>Ru.

In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, <sup>177</sup>Lu, <sup>80</sup>Y, <sup>164</sup>Ho, and <sup>135</sup>Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is <sup>111</sup>In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is <sup>164</sup>Y. In specific embodiments, the macrocyclic chelator is 1.4,7,10-tetraazacyclododecane-N,N\*,N\*,N\*\*-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0260] As mentioned, the proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be eyelic, with or without branching. Cyclic, branched, and branched eyelic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include accelylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking,

cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of proglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, premylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS-STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifler et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

102611 Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties. The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0263] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., Appl. Biochem. Biotechnol. 56:59-72 (1996; Vorobjev et al., Nucleosides Nucleotides 18:2745-2750 (1999); and Caliceti et al., Bioconjug. Chem. 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0264] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0.401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be

bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0265] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein. [0266] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol

polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated protein in the method of molecules if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminals modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0267] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkeriess systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

10268] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of momethoxy polyethylene glycol (MPEG) using tresylchloride (CISO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

10269] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0270] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

10271] The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0272] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in ATCCT<sup>IM</sup> Deposit No:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing three polypeptides having identical or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotertamer.

[0274] As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heteroteramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer or at least a heterotrimer.

[0275] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in ATCC™ Deposit No; Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5.478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat, No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0276] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or

trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

10277] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. 
Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One 
example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. 
(FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by 
reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing 
trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between FLAG® polypeptide sequence (Asp-Tyr-Lys-Asp-Asp-Asp-Lys) contained in fusion proteins of the invention. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in FLAG® fusion proteins of the invention and anti-FLAG® antibody. The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

notation and the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[0281] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEO ID NO:Y or a polypeptide encoded by the cDNA contained in ATCC™ Deposit No:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain nutbodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CHI, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CHI, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in U.S. Patent No. 5393.598 by Kucherlapati et al.

10283] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148; 1547-1553 (1992).

[0284] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in continuous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include the predicted epitopes shown in Table IB, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

102851 Antibodies of the present invention may also be described or specified in terms of their crossreactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10<sup>-2</sup> M, 10<sup>-2</sup> M, 5 X 10<sup>-3</sup> M, 10<sup>-3</sup> M, 5 X 10<sup>-4</sup> M, 10<sup>-4</sup> M, 5 X  $10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$ M,  $5 \times 10^{-7}$  M,  $10^{7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M, 5 X  $10^{-11}$  M,  $10^{-11}$  M, 5 X  $10^{-12}$  M,  $10^{-12}$  M, 5 X  $10^{-13}$  M,  $10^{-13}$  M, 5 X  $10^{-14}$  M,  $10^{-14}$  M, 5 X  $10^{-15}$  M, or 10<sup>-15</sup> M

[0286] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 80%, at least 80%, at least 80%, at least 70%, at least 50%.

no nuisbodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described surera). In specific embodiments, antibodies are provided that inhibit ligand

activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and [0288] receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998): Yoon et al., J. Immunol, 160(7):3170-3179 (1998): Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998): Pitard et al., J. Immunol, Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[0289] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both in witro and in vivo diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

10290] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. Sec. e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incomporated herein by reference in their entircties.

10291] The antibodies of the invention include derivatives that are modified, i.e. by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be

carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

no. 1022] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and plage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

10294] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCCTM. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention. [0296] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current

Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood. but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV. In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks, A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCCTM #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g. SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells. Antibody fragments which recognize specific epitopes may be generated by known techniques. [0298] For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[0299] For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol, Methods 182:41-50 (1995); Ames et al., J. Immunol, Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5.698.426; 5.223.409; 5.403.484; 5.580.717; 5.427.908; 5.750.753;

5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

(n940) As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92:22334; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their emireties).

103011 Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991): Shu et al., PNAS 90:7995-7999 (1993): and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol, Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter. preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0302] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0303] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes, For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol, 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5.885,793; 5.916,771; 5.939,598; 6.075,181; and 6.114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above

[0304] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same entipore. General al., Bio/echnology 12:899-903 (1988)).

[10305] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate antiidiotype antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled
in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol.

147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide
multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate antiidiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind
to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such
anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand(s)/receptor(s). For
example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its
ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and
enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or

signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

[0306] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:995-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

## Polynucleotides Encoding Antibodies

[0307] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in ATCC<sup>TM</sup> Deposit No:Z.

[0308] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[10309] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3° and 5° ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0310] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Aussibel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

103111 In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0312] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

10313] Alternatively, techniques described for the production of single chain antibodies (U.S. Parent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038-1041 (1988)).

Methods of Producing Antibodies

[0314] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

[0315] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0316] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polymacleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoalobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules [0317] of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter, the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukarvotic cells, especially for the expression of whole recombinant antibody molecule, are used for the

expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovins is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8.2 (1990)).

103181 In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety. In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in Spodoptera frugiperda cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)). In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end.

eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 373, W138, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7903 and Hs578Bst.

103221 For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule. A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48;202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg. Proc. Natl. Acad. Sci. USA 78:2072 (1981)): neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshey, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

10324] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is

associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol., 3:257 (1983)).

10325] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell lines (e.g., the murine mycloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expression gells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from supliliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodics using a GS expression system in murine mycloma cells is described in Bebbington et al., Bio/technology 10:169(1992) and in Biblia and Robinson Biotechnol. Prog. 11:1 (1995) which are incorporated in their entirities by reference herein.

10326] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322.52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0327] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0328] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention to antibodies of the present invention may also be used in in vitro immunoassays and purification methods

using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439.095; Naramura et al., Immunol, Lett. 39.91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

10329] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fe region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CHI domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fe portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fe portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenza'c et al., Proc. Natl. Acad. Sci. USA 88:10335-10539 (1991); Zheng et al., J. Immunol. 1544:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

[0330] As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEO ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polyneptides corresponding to SEO ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; and Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis. and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

[0331] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue. Chatsworth. CA. 91311). among others, many of which are commercially available. As described

in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "FLAG®" tag (Asp-Tyr-Lys-Asp-Asp-Asp-Lys). 103321 The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycocrythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and acquorin; and examples of suitable

10333] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alphaemitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-flutoruracil decarbazine), alkylating agents (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-flutoruracil decarbazine), alkylating agents (e.g., methotrethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclottosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunombicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin, bleomycin, mithramycin, and anthramycin (AMCI)), and anti-mitotic agents (e.g., vincristine and vinblastine).

radioactive material include 125L 131L 111In, or 99Tc.

10334] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, B-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/3389), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0335] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

10336] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Armon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0337] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0338] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[0339] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the gene of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison et al., Cell. 96:737-49 (1999)).

[0340] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-sell" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoictic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

10.341 The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunossasys which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunosasys, ELISA (enzyminked immunosorbent assay), "sandwich" immunosasys, immunoprecipitation assays, precipitin reactions, gel difflusion precipitin reactions, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausside et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphates and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose heads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausuhel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

Mestern blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or nonfat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

IELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Aussibel et al., eds. (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

10345] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 1251) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 1251) in the presence of increasing amounts of an unlabeled second antibody.

[0346] Antibodies of the invention may be characterized using immunocytochemisty methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the expression of an antigen or with vector alone using techniques commonly known in the art. Antibodies that bind antigen transfected cells, but not vector-only transfected cells, are antigen specific.

#### Theraneutic Uses

10347] Table ID also provides information regarding biological activities and preferred then-peutic uses (i.e. see, "Preferred Indications" column) for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table ID also provides information regarding assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA ATCCTM Deposit No."2") provides the unique clone identifier for each clone as previously described and indicated in Table 1A, Table 1B, and Table 1C. The third column ("AA SEQ ID NO."4") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Table 1A, Table 1B, and Table 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity.

[0348] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-diotypic antibodies as described herein). The antibodies of the invention can be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate diseases, disorders or conditions associated with abermant expression and/or activity of a polypeptide of the invention, including, but not limited to, diabetes mellitus. The treatment and/or prevention of diabetes mellitus associated with abermant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with diabetes mellitus. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

10.349 In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating diabetes mellitus. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a polypeptide of the invention (such as, for example, a predicted linear epitope shown in Table 1B; or a conformational epitope, including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to detect, diagnose, prevent, treat, prognosticate, and/or ameliorate diabetes mellitus or conditions associated with aberrant expression and/or activity of a polypeptide of the invention. The treatment and/or prevention of diabetes mellitus or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0350] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0351] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0352] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diabetes mellitus related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than  $5 \times 10^2 \text{ M}$ ,  $10^2 \text{ M}$ ,  $5 \times 10^3 \text{ M}$ ,  $10^3 \text{ M}$ ,  $5 \times 10^4 \text{ M}$ ,  $10^5 \text{ M}$ ,  $5 \times 10^5 \text{ M}$ ,  $10^5 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 \text{ M}$ ,  $5 \times 10^6 \text{ M}$ ,  $10^6 

Gene Therapy

[0354] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a diabetes mellitus associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0355] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0356] For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

no357] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijistra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[9388] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy. [0359] In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In vet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO 92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Ziilstra et al., Nature 342:435-438 (1989). [0360] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an

antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

(19361) Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenovirus-based we the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0362] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204;289-300 (1993); U.S. Patent No. 5,436,146).

[0.363] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection.
Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene.
Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

(9365) The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blond cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

(19366) Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0367] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0368] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71-973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittlekow and Soott, Mavo Clinic Proc. 61:771 (1986).

[0369] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

10370] The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[0371] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, does, etc., and is preferably a mammal, and most preferably human.

[0372] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0373] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizine agent.

[0374] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0375] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[0376] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sethon, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

[0377] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0.378] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0379] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, tale, sodium elhoride, dried skim milk, glycerol, propylene, glycol, water,

ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are deserribed in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0380] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by influsion, it can be dispensed with an influsion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0381] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tataria eaids, etc., and those formed with eations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamine ethanol, histidine, procaine, etc.

[0382] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with abernant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[0383] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies

of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

10.844 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the asency of manufacture, use or sale for human administration.

### Diagnosis and Imaging

10385] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, prognosticate, or monitor diabetes mellitus and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

10386] The invention provides a diagnostic assay for diagnosing diabetes mellitus, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of diabetes mellitus. With respect to insulin resistance, the presence of a relatively high or low amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of insulin resistance into diabetes mellitus.

10387] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 1015/3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (1251, 1211), carbon (14C), sulfur (35S), tritium (3H), indium (112in), and technetium (99Te); luminescent labels, such as fluorescein and rhodamine, and biotin.

[0388] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering

for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background levely, c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

(0.89) It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTe. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0390] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0391] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0392] Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0393] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[0394] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polymacleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0396] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporterlabeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0397] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polymucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0398] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0399] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0400] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled antihuman antibody for detecting surface-bound anti-antigen antibody.

#### Uses of the Polynucleotides

[0401] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[19402] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1B.1, column 8 provides the chromosome location of some of the polynucleotides of the invention.

[9403] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an annulified fragment.

194041 Similarly, somatic hybrids provide a rapid method of PCR mapping the polymucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e. e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incomporated by reference in its entirety).

[0408] Precise chromosomal location of the polymucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polymucleotides as short as 500 or 600 bases; however, polymucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0406] For chromosome mapping, the polynticleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[0407] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1B and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[0408] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

10409] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library)). Column 9 of Table 1B.1 provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1B.1, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 notential causative genes.

10410] Thus, once coinheritance is established, differences in a polymucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are secretained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

104411. Furthermore, increased or decreased expression of the gene in affected individuals as command.

[0411] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polymucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assaws", and "Methods for Detecting Diseases").

10412] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[0413] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[0414] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level

19415] By "measuring the expression level of polymucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used reneatedly as a standard for comparison.

[0416] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as seen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0417] The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polymucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with ophynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pullmonary disorders, digestive disorders, metabolic disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

[0418] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art.

The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254, 1497 (1991); and Egholm et al., Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[0419] The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplassias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and ethronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0420] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplastics are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

[0421] For example, c-mye expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-mye is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5° end of c-mye or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-mye or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, and/or prognosis of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

104221 In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem, 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem, 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Nonlimiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods", and Examples 16, 17 and 18).

10424] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0425] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These secuences can be used to presare PCR primers for amplifying and isolating such selected DNA, which can

then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples. Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DOa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992)). Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes. There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to those shown in Table 1B. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen

10428] The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunostytochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, those disclosed in Table 1B, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

tissue cultures for contamination. Additional non-limiting examples of such uses are further described

[0429] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[0430] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antien to elicit an immune response.

Uses of the Polypeptides

herein

[0431] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0432] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0433] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunoassay (BLIAS) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (1311, 1251, 1271), carbon (14°C), sulfur (28°S), tritium (21H), indium (1156°In, 1156°In, 1156°

In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131, 112In, 99mTc, (131 I, 125I, 123I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (115mIn, 113mIn, 112In, 111In), and technetium (99Tc, 99mTc), thallium (201 Ti), gallium (68 Ga, 67 Ga), palladium (103 Pd), molybdenum (99 Mo), xenon (133 Xe), fluorine (18 F, 153 Sm, <sup>177</sup>Lu. <sup>159</sup>Gd. <sup>149</sup>Pm. <sup>140</sup>La. <sup>175</sup>Yb. <sup>166</sup>Ho. <sup>90</sup>Y. <sup>47</sup>Sc. <sup>186</sup>Re. <sup>188</sup>Re. <sup>142</sup>Pr. <sup>105</sup>Rh. <sup>97</sup>Ru), a radio-opaque substance. or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0436] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0437] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of lumor cells) by administering polypeptides of the invention in association with toxins or evotoxic prodruss.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, Pseudomonas exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin, "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi, or other radioisotopes such as, for example, 103Pd, 133Xe, 131I, 68Ge, 57Co, 65Zn, <sup>85</sup>Sr, <sup>32</sup>P, <sup>35</sup>S, <sup>90</sup>Y, <sup>153</sup>Sm, <sup>153</sup>Gd, <sup>169</sup>Yb, <sup>51</sup>Cr, <sup>54</sup>Mn, <sup>75</sup>Se, <sup>113</sup>Sn, <sup>90</sup>Yttrium, <sup>117</sup>Tin, <sup>186</sup>Rhenium, <sup>166</sup>Holmium, and 188Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope 90Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope 111 In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope 131I.

[0439] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0440] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more

definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gestrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0442] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[0443] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

# Diagnostic Assays

10444] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in manuals, preferably humans. Such disorders include, but are not limited to, those related to biological activities described in Table 1D and, also as described herein under the section headine "Biological Activities".

19445] For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding the polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed in vivo or in vitro, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

[0446] The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0447] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognosticate diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

10448] By "assaying the expression level of the gene encoding the polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individual not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0449] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0450] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomezynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

10451 The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of polypeptides of the invention compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

[0452] Assaying polypeptide levels in a biological sample can occur using antibody-based techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987)).

Other antibody-based methods useful for detecting polypeptide gene expression include immunossasys, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunosasay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (<sup>125</sup>I, <sup>121</sup>I), carbon (<sup>14</sup>C), sulfur (<sup>35</sup>S), tritium (<sup>21</sup>H), indium (<sup>112</sup>In), and technetium (<sup>35o</sup>Te), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0453] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of inteest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

For example, antibodies, or fragments of antibodies, such as those described herein, may be [0454] used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection. 104551 In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the polypeptides of the invention (shown in Table 1B) may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection. 104561 In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a polypeptide of the invention may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0457] The antibodies (or fragments thereof), and/or polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of gene products or conserved variants or peptide fragments hereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The antibody (or fragment thereof) or polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the gene product, or conserved variants or peptide fragments, or polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0458] Immunoassays and non-immunoassays for gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art. [0459] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled antibody or detectable polypeptide of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally

the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by

conventional means.

[0460] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0461] The binding activity of a given lot of antibody or antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

In addition to assaying polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, polypeptide or polynucleotide can also be detected in vivo by imaging. For example, in one embodiment of the invention, polypeptides and/or antibodies of the invention are used to image diseased cells, such as neoplasms. In another embodiment, polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of an mRNA) and/or antibodies (e.g., antibodies directed to any one or a combination of the epitopes of a polypeptide of the invention, antibodies directed to a conformational epitope of a polypeptide of the invention, or antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells.

[0463] Antibody labels or markers for in vivo imaging of polypeptides of the invention include those detectable by X-radiography, NMR, MRI, CAT-seans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where in vivo imaging is used to detect enhanced levels of polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for

producing chimeric antibodies are known in the art. See, for review, Morrison, Science 229:1202 (1985). Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).

[0464] Additionally, any polypeptides of the invention whose presence can be detected, can be administered. For example, polypeptides of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized in vivo, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for in vitro diagnostic procedures.

notes A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112 n, 50m TC), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 50m Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the antigenic protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson

Publishing Inc. (1982)).

104661 With respect to antibodies, one of the ways in which an antibody of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., J. Clin. Pathol. 31:507-520 (1978); Butler, J.E., Meth. Enzymol. 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alphaglycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0467] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect polypeptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[4468] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescent isothiocyanate, rhodamine, phycocyythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescennine.

[0469] The antibody can also be detectably labeled using fluorescence emitting metals such as <sup>152</sup>Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0470] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[4471] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and acquorin.

#### Methods for Detecting Diseases

[0472] In general, a disease may be detected in a patient based on the presence of one or more proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a disease or disorder, including cancer and/or as described elsewhere herein. In addition, such proteins may be useful for the detection of other diseases and cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding polypeptides of the invention, which is also indicative of the presence or absence of a disease or disorder, including cancer. In general, polypeptides of the invention should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

10473] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, supra. In general, the presence or a disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

10474 In a preferred embodiment, the assay involves the use of a binding agent(s) immobilized on a solid support to bind to and remove the polypeptide of the invention from the remainder of the sample. The

bound polypeptide may then be detected using a detection reagent that contains a reporter group and

specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include polypeptides of the invention and portions thereof, or antibodies, to which the binding agent thinds, as described above.

104751 The solid support may be any material known to those of skill in the art to which polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[0476] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

# Gene Therapy Methods

[0477] Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, W090/11092, which is herein incorporated by reference.

10478] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993; Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0479] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0480] In one embodiment, the polymucleotide of the present invention is delivered as a naked polymucleotide. The term "naked" polymucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polymucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

10481] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication.

Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0482] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter, or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothonein promoter, the shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter, retroviral LTRs; the b-actin promoter, and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[0483] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polyneptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thyrmus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, clastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated relies, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0485] For the naked nucleic acid sequence injection, an effective dossage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dossage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 25 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dossage will vary according to the tissue site of injection. The appropriate and effective dossage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

10486] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0487] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0488] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0489] In certain embodiments, the polynacleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference); in functional form. [0490] Cationic liposomes are readily available. For example,

N[1-2,3-dioleyloxy)propyl]-N,N,N-trichylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Bochringer). [0491] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare linosomes from other cationic lipid materials.

[16492] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for makine liposomes using these materials are well known in the art.

[0493] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unlamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca<sup>23</sup>-EDTA

chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394-483; Wilson et al., Cell 17:77 (1979); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443-629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982), which are herein incorporated by reference.

[6495] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0496] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0497] In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

10498] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO4 precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0499] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polyneptide of the present invention.

[16500] In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore,

adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al. Am. Rev. Respir. Dis. 1092.33-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 36:5691-692 (1993); and U.S., Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

19502] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0503] In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyezka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5.139.941. 5.173.414. 5.354.678. 5.476.146. 5.474.935. 5.478.745. and 5.589.377.

[9804] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Mother method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342-345-438 (1989), which are herein encorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0507] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

16508] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0509] The promoter-targetting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0510] The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5° end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0511] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0512] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[05.13] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

10514 Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

[0515] Preferred methods of systemic administration, include intravenous injection, acrosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Acrosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

105161 Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0517] Therapeutic compositions of the present invention can be administered to any animal, preferably to manimals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pies, with humans being particularly preferred.

# **Biological Activities**

[0518] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

[0519] Members of the secreted family of proteins are believed to be involved in biological activities associated with, for example, cellular signaling. Accordingly, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders associated with aberrant activity of secreted polypeptides.

[0520] In preferred embodiments, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, prognosis, prevention, treatment, and/or amelioration of diseases and/or disorders relating to diabetes mellitus and/or a condition associated with diabetes mellitus (e.g., hyperglycemia, obesity, diabetic retinopathy, mononeuropathy, polyneuropathy, atherosclerosis, theers, heart disease, anemia, stroke, gangrene (e.g., of the feet and hands), impotence, infection, cataract, poor kidney function, malfunctioning of the autonomic nervous system, impaired white blood cell function, Carpal tunnel syndrome, Dupuytren's contracture, diabetic ketoacidosis, and as described in "Renal Disorders", "Wound Healing and Epithelial Cell Proliferation", "Endocrine Disorders", "Reproductive System Disorders", and "Gastrointestinal Disorders" sections below).

[0521] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognosticate diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

[0522] Thus, polynucleotides, translation products and antibodies of the invention are useful in the diagnosis, detection, prevention, prognisication, and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, prohormone activation, neurotransmitter activity, cellular signaling, cellular proliferation, cellular differentiation, and cell migration.

16523] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, treatment and/or amelioration of diseases and/or disorders associated with the following system or systems.

# Renal Disorders

[9544] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate disorders of the renal system. Renal disorders which can be detected, prevented, diagnosed, prognosticated, treated, and/or ameliorated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, selerosis and necrosis, electrolyte imbalance, and kidney cancers.

[9525] Kidney diseases which can be detected, prevented, diagnosed, prognosticated, treated, and/or ameliorated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis.

nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, chronic ubulointerstitial nephritis, chronic tubulointerstitial nephritis, chronic post-streptococcal glomerulonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis, blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

[0526] In addition, compositions of the invention can be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartrup disease, Bartter's syndrome, cilddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoc kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy, and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

[0827] Compositions of the invention can also be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate selerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydrorephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hyperalcemia, hypophosphatemia, and hyperphosphatemia).

[9528] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, acrosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

## Wound Healing and Epithelial Cell Proliferation

[0529] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate thair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial tlucers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

10530] Polymucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polymucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fiscia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

105311 It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[9533] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating recpithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat eastric and doudenal ulcers and help heal by sear formation of the mucosal lining and

regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

[0534] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

[9635] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[0536] In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

## **Endocrine Disorders**

[0537] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

10.538] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone

imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polymeleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

16339] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, postterm pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[19540] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes inspidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, aeromegaly, gigantism, disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis). Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism, disorders and/or diseases of the hypothalanus.

[0541] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome and anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoolasias of the testis and neo-testis.

10842] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, phecohromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[0843] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

### Reproductive System Disorders

[0544] The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases and/or

disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[0545] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, variocede, spermatocele, inguinal hemia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

10546] Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatos, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, dictal carcinomas, and sonamous cell carcinomas.

10547] Additionally, the compositions of the invention may be useful in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma actuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronic's disease, crecitie dysfunction, and impotence.

104.54] Moreover, diseases and/or disorders of the vas deferens include vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases and disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[0549] Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[9650] Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the detection, prevention, diagnosis, prognostication, treatment, and/or ambitoration of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale. Imphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen selerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvoragetiis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intracpithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorthea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorthea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of congenital uterine abnormalities, such as bicomutate uterus, septate uterus, simple unicormutate uterus with a noneavitary rudimentary horn, unicormutate uterus with a non-communicating cavitary rudimentary born, unicormutate uterus with a communicating cavitary non, arcuate uterus, uterine didelfus, and T-shaped uterus.

[0852] Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[0853] Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[0554] Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and sentic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

[0555] Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding. [0556] Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus. [0557] Other disorders and/or diseases of the female reproductive system that may be detected, prevented, diagnosed, prognosticated, treated, and/or ameliorated by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory diseases, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

### Gastrointestinal Disorders

[0558] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate gastrointestinal diseases and disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

(0559) Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the sophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stormach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Menétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess.).

[0560] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (Ascariasis lumbricoides), Hookworms (Ancylostoma duodenale), Threadworms (Enterobius vermicularis), Tapeworms (Taenia sazinata Echinococcus granulosus, Dinhyllosothrium spn., and T. solium).

[0861] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (sosphageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, evstic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphomal), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome). Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute 105621 necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[0563] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

0564] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, absecsses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, loudenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (filea neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal poplasms, (eccal neoplasms, colonic neoplasms, duodenal neoplasms, iteal neoplasms, intestinal poplasms, proparome, duodenal dostruction, impacted feces, intestinal pseudo-obstruction

[cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-ieghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis. Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

## Chemotaxis

[9566] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[0567] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location.
Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds

[0588] It is also contemplated that polymeleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polymeleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

#### Binding Activity

[0559] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., recenturs) for small molecules.

[0570] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[0571] Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[0572] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

(10573) Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[0574] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substate.

[0875] Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are

exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinsse.

[0576] Following fixation and incubation, the slides are subjected to auto-radiographic analysis.
Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[0577] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[0578] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codonshuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. See generally, U.S. Patent Nos. 5.605,793, 5.811.238, 5.830,721. 5.834,252, and 5.837,458, and Patten, P. A., et al., Curr. Opinion Biotechnol, 8:724-33 (1997); Harayama, S. Trends Biotechnol. 16(2):76-82 (1998); Hansson, L. O., et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. Biotechniques 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polyneptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibinalpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF). Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypertide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0580] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and <sup>3</sup>[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to the amount of fibroblast proliferation in the presence of the compound to determine if the compound to the amount of substantial proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of <sup>3</sup>[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of <sup>3</sup>[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

10881 In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinostitide hydrolysis.

[0882] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

[0883] Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonitss/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

## Targeted Delivery

[0584] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

10888] As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydropholic, indicand/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[6886] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclesse, RNAse, alpha toxin, ricin, abrin, Pseudomonas exotoxin A, diptheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mittomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

### Drug Screening

19888] Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaving the activity of these polypeptides following binding.

10889] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

[6890] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

[0591] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[0892] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the artibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

## Antisense And Ribozyme (Antagonists)

ines93] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA ATCC\*\*\* Deposit No:Z identified for example, in Table 1A and/or 1B. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Comor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-mye and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCI pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

[6959] For example, the 5<sup>t</sup> coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide. nose in one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982), etc.

16897] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

015gonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides. at least 17 nucleotides at least 17 nucleotides.

[0599] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule.

hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptions in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556, Lemaitre et al., 1987, Proc. Natl. Acad. Sci. W.S.A. 86:6553-6556, Lemaitre et al., 1987, or the blood-brain barrier (see, e.g., PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO88/010134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl2-thiouridine, 5-carboxymethylaminomethyluracil, dilydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylguanine, 2-methylguanine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 2-methyladenine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5-methylaminomethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiouracil, 2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, acetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyluracil, 5-methyluracil, 5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyluracil, 5-methyluracil, 5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyluracil, 5-methyluracil, 5-oxyacetic acid delphyladenic, uracil-5-oxyacetic acid (v), 5-methyluracil, 5-methyluracil, 5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyluracil, 5-methyluracil, 5-methyluracil,

[0601] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[0602] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

[0605] While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred. [1666] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (Sec. e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al., Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNA catalogue of the locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5\*-UG-3\*. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5\* end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[0607] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[6608] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

16699 The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

[0610] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[0611] The antagonist/agonist may also be employed to treat the diseases described herein.

[0612] Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention

## Binding Peptides and Other Molecules

[0613] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[0614] This method comprises the steps of: contacting polypeptides of the invention with a plurality of molecules; and identifying a molecule that binds the polypeptides of the invention.

10615] The step of contacting the polypeptides of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptides of the invention. The molecules having a selective affinity for the polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptides of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptides and the individual clone. Prior to contacting the polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for polypeptides of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptides of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypoptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

[0617] In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of the polypeptides of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptides of the invention or the plurality of polypeptides are bound to a solid support.

[10618] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind polypeptides of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991,

Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383. 19619 

Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/1818 flated Aug. 18, 1994.

[0620] In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91-9072-9076

[0621] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-1142).

[0622] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

196231 Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the henzodiazenine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[0625] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e. g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Standt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tueric et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852;
U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94:18318.

[0626] In a specific embodiment, screening to identify a molecule that binds polypeptides of the invention can be carried out by contacting the library members with polypeptides of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptides of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

[0627] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to polypeptides of the invention.

[0628] Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case pentides.

10629 Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

10630] As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 1.5-100 amino acids, or 20-50 amino acids.

[0631] The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

## Other Activities

[1652] A polypeptide, polymucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating revascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polymucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[1653] A polypeptide, polymucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are

mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[0634] A polypeptide, polymucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[0635] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

10636] A polypeptide, polymucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polymucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[0637] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[0638] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematonoicite linease.

10639] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[0640] A polypeptide, polymucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[0641] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[1642] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments the host is a human

#### Other Preferred Embodiments

[0643] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC<sup>M</sup> Deposit No.Z.

[0644] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO.X as defined in column 5, "ORF (From-To)", in Table 1B.1.

[0645] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in columns 8 and 9, "NT From" and "NT To" respectively. in Table 2.

10646] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCCT<sup>TM</sup> Deposit No:Z.

[9647] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC<sup>TM</sup> Denosit No:Z.

[0648] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in column 5 "ORF (From-To)" in Table 1B 1

[0649] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in columns 8 and 9. "NT From" and "NT To", respectively, in Table 2.

[10650] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID No.X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1.0 r columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC™ Deposit No.Z. [10651] Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO.X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC™ Deposit No.Z, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only Tresidues.

[0652] Also preferred is a composition of matter comprising a DNA molecule which comprises the cDNA contained in ATCC™ Deposit No;Z.

[0653] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides of the cDNA sequence contained in ATCCT Deposit No.Z.

[0654] Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by cDNA contained in ATCCT<sup>M</sup> Deposit No.Z.

[16655] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in ATCCTM Deposit No.Z.

[0656] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in ATCC™ Deposit No:Z.

[0657] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by cDNA contained in ATCC™ Denosit No.Z.

Inot891 A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in ATCC™ Deposit No:Z; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

[0659] Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[1666] A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting mucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of the cDNA contained in ATCCT\*\* Deposit No:Z.

[0661] The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Mos preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; or the cDNA contained in ATCC<sup>M</sup> Deposit No:Z which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of cDNA contained in ATCC<sup>M</sup> Deposit No:Z.

196631 The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Moso preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table IB.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in ATCCTM Deposit No:Z. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

10665] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000, or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence or SEQ ID NO:X wherein X is any integer as defined in Table I A and/or IB; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA "Clone ID" in Table IA and/or IB.

Mso preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO.Y; a polypeptide encoded by SEQ ID NO.X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCCTM Deposit No.Z.

Maso preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO.Y; a polypeptide encoded by SEQ ID NO.X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCCTM Deposit No.Z.

[10688] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the mucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCCTM Denosit No:Z.

[9669] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO.Y.; a polypeptide encoded by SEQ ID NO.X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCCTM Deposit No.Z. [9670] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90%

identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by contained in ATCC $^{TM}$  Deposit No:Z

[0671] Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by cDNA contained in ATCC<sup>TM</sup> Deposit No.Z; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or the polypeptide sequence of SEQ ID NO:Y.

[0672] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA contained in ATCC™ Deposit No.Z.

[0673] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA contained in ATCCTM Deposit No.Z.

106741 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA contained in ATCCT<sup>TM</sup> Deposit No.Z.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC<sup>TM</sup> Perosit No:Z.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO.Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCCTM Deposit No:Z; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

[0677] Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:X; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC<sup>MD</sup> Peposit No:Z.

[0678] Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

0679] Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:Y or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC<sup>TM</sup> Deposit No:Z.

[0680] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1A, 1B or Table 2 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC<sup>ND</sup> Deposit No:Z.

[0682] In any of these methods, the step of detecting said polypeptide molecules includes using an antibody. Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC<sup>TM</sup> Deposit No:Z.

[0684] Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

10685] Also preferred is a polypeptide molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO.Y; a polypeptide encoded by SEQ ID NO.X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC<sup>TM</sup> Deposit No.Z.

19686] Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

10687] Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCCTM Deposit NO:Z. The isolated polypeptide produced by this method is also preferred.

[0688] Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polymucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

[16690] Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., tumors, leukemias or lymphomas), which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide of the

invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

[0691] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

# Description of Table 6

[16692] Table 6 summarizes some of the ATCCT<sup>TM</sup> Deposits, Deposit dates, and ATCCT<sup>TM</sup> designation numbers of deposits made with the ATCCT<sup>TM</sup> in connection with the present application. These deposits were made in addition to those described in the Table 1A.

Table 6

| ATCCTM Deposits         | Deposit Date | ATCCTM Designation Number                       |
|-------------------------|--------------|-------------------------------------------------|
| LP01, LP02, LP03, LP04, | May-20-97    | 209059, 209060, 209061, 209062, 209063, 209064, |
| LP05, LP06, LP07, LP08, |              | 209065, 209066, 209067, 209068, 209069          |
| LP09, LP10, LP11,       |              |                                                 |
| LP12                    | Jan-12-98    | 209579                                          |
| LP13                    | Jan-12-98    | 209578                                          |
| LP14                    | Jul-16-98    | 203067                                          |
| LP15                    | Jul-16-98    | 203068                                          |
| LP16                    | Feb-1-99     | 203609                                          |
| LP17                    | Feb-1-99     | 203610                                          |
| LP20                    | Nov-17-98    | 203485                                          |
| LP21                    | Jun-18-99    | PTA-252                                         |
| LP22                    | Jun-18-99    | PTA-253                                         |
| LP23                    | Dec-22-99    | PTA-1081                                        |

## Examples

# Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

[6693] Each ATCC<sup>TM</sup> Deposit No.Z is contained in a plasmid vector. Table 7 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been existed. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 7 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

| Vector Used to Construct Library | Corresponding Deposited Plasmid |
|----------------------------------|---------------------------------|
| Lambda Zap                       | pBluescript (pBS)               |
| Uni-Zap XR                       | pBluescript (pBS)               |
| Zap Express                      | pBK                             |
| lafmid BA                        | plafmid BA                      |
| pSport1                          | pSport1                         |
| pCMVSport 2.0                    | pCMVSport 2.0                   |
| pCMVSport 3.0                    | pCMVSport 3.0                   |
| pCR®2.1                          | pCR <sup>®</sup> 2.1            |

[16694] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Eap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988), Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037, pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for Kpul which are the first sites on each respective end of the linker). "+" or "." refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

[6695] Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993)). Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR\*2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlshad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., BioTechnology 9: (1991)). Preferably, a polynucleotide of the present invention does not comprise the

phage vector sequences identified for the particular clone in Table 7, as well as the corresponding plasmid vector sequences designated above.

[16696] The deposited material in the sample assigned the ATCC<sup>™</sup> Deposit Number cited by reference to Table 1A, Table 2, Table 6 and Table 7 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC<sup>™</sup> Deposit Number contain at least a plasmid for each ATCC<sup>™</sup> Deposit No.Z.

TABLE 7

| Libraries owned by Catalog                                   | Catalog Description                                        | Vector        | ATCCTM  |
|--------------------------------------------------------------|------------------------------------------------------------|---------------|---------|
|                                                              |                                                            |               | Deposit |
| HUKA HUKB HUKC HUKD<br>HUKE HUKF HUKG                        | Human Uterine Cancer                                       | Lambda ZAP II | LP01    |
| HCNA HCNB                                                    | Human Colon                                                | Lambda Zap II | LP01    |
| HFFA                                                         | Human Fetal Brain, random primed                           | Lambda Zap II | LP01    |
| HTWA                                                         | Resting T-Cell                                             | Lambda ZAP II | LP01    |
| HBQA                                                         | Early Stage Human Brain, random<br>primed                  | Lambda ZAP II | LP01    |
| HLMB HLMF HLMG HLMH<br>HLMI HLMJ HLMM HLMN                   | breast lymph node CDNA library                             | Lambda ZAP II | LP01    |
| HCQA HCQB                                                    | human colon cancer                                         | Lamda ZAP II  | LP01    |
| HMEA HMEC HMED HMEE<br>HMEF HMEG HMEI HMEJ<br>HMEK HMEL      | Human Microvascular Endothelial<br>Cells, fract. A         | Lambda ZAP II | LP01    |
| HUSA HUSC                                                    | Human Umbilical Vein Endothelial<br>Cells, fract. A        | Lambda ZAP II | LP01    |
| HLQA HLQB                                                    | Hepatocellular Tumor                                       | Lambda ZAP II | LP01    |
| HHGA HHGB HHGC HHGD                                          | Hemangiopericytoma                                         | Lambda ZAP II | LP01    |
| HSDM                                                         | Human Striatum Depression, re-<br>rescue                   | Lambda ZAP II | LP01    |
| HUSH                                                         | H Umbilical Vein Endothelial Cells,<br>frac A, re-excision | Lambda ZAP II | LP01    |
| HSGS                                                         | Salivary gland, subtracted                                 | Lambda ZAP II | LP01    |
| HFXA HFXB HFXC HFXD HFXE<br>HFXF HFXG HFXH                   | Brain frontal cortex                                       | Lambda ZAP II | LP01    |
| HPQA HPQB HPQC                                               | PERM TF274                                                 | Lambda ZAP II | LP01    |
| HFXJ HFXK                                                    | Brain Frontal Cortex, re-excision                          | Lambda ZAP II | LP01    |
| HCWA HCWB HCWC HCWD<br>HCWE HCWF HCWG HCWH<br>HCWI HCWJ HCWK | CD34 positive cells (Cord Blood)                           | ZAP Express   | LP02    |
| HCUA HCUB HCUC                                               | CD34 depleted Buffy Coat (Cord<br>Blood)                   | ZAP Express   | LP02    |
| HRSM                                                         | A-14 cell line                                             | ZAP Express   | LP02    |
| HRSA                                                         | A1-CELL LINE                                               | ZAP Express   | LP02    |
| HCUD HCUE HCUF HCUG<br>HCUH HCUI                             | CD34 depleted Buffy Coat (Cord<br>Blood), re-excision      | ZAP Express   | LP02    |
| HBXE HBXF HBXG                                               | H. Whole Brain #2, re-excision                             | ZAP Express   | LP02    |
| HRLM                                                         | L8 cell line                                               | ZAP Express   | LP02    |
| HBXA HBXB HBXC HBXD                                          | Human Whole Brain #2 - Oligo dT<br>> 1.5Kb                 | ZAP Express   | LP02    |
| HUDA HUDB HUDC                                               | Testes                                                     | ZAP Express   | LP02    |
| HHTM HHTN HHTO                                               | H. hypothalamus, frac A;re-excision                        | ZAP Express   | LP02    |
| HHTL                                                         | H. hypothalamus, frac A                                    | ZAP Express   | LP02    |

| Libraries owned by Catalog                                   | Catalog Description                      | Vector     | ATCCTM  |
|--------------------------------------------------------------|------------------------------------------|------------|---------|
| Distances owned by Camalog                                   | Cumandy Description                      | redioi     | Deposit |
| HASA HASD                                                    | Human Adult Spleen                       | Uni-ZAP XR | LP03    |
| HFKC HFKD HFKE HFKF HFKG                                     | Human Fetal Kidney                       | Uni-ZAP XR | LP03    |
| HE8A HE8B HE8C HE8D HE8E<br>HE8F HE8M HE8N                   | Human 8 Week Whole Embryo                | Uni-ZAP XR | LP03    |
| HGBA HGBD HGBE HGBF<br>HGBG HGBH HGBI                        | Human Gall Bladder                       | Uni-ZAP XR | LP03    |
| HLHA HLHB HLHC HLHD HLHE<br>HLHF HLHG HLHH HLHQ              | Human Fetal Lung III                     | Uni-ZAP XR | LP03    |
| HPMA HPMB HPMC HPMD<br>HPME HPMF HPMG HPMH                   | Human Placenta                           | Uni-ZAP XR | LP03    |
| HPRA HPRB HPRC HPRD                                          | Human Prostate                           | Uni-ZAP XR | LP03    |
| HSIA HSIC HSID HSIE                                          | Human Adult Small Intestine              | Uni-ZAP XR | LP03    |
| HTEA HTEB HTEC HTED HTEE<br>HTEF HTEG HTEH HTEI HTEJ<br>HTEK | Human Testes                             | Uni-ZAP XR | LP03    |
| НТРА НТРВ НТРС НТРО НТРЕ                                     | Human Pancreas Tumor                     | Uni-ZAP XR | LP03    |
| HTTA HTTB HTTC HTTD HTTE<br>HTTF                             | Human Testes Tumor                       | Uni-ZAP XR | LP03    |
| НАРА НАРВ НАРС НАРМ                                          | Human Adult Pulmonary                    | Uni-ZAP XR | LP03    |
| HETA HETB HETC HETD HETE<br>HETF HETG HETH HETI              | Human Endometrial Tumor                  | Uni-ZAP XR | LP03    |
| ННГВ ННГС ННГО ННГЕ ННГГ<br>ННГС ННГН ННГІ                   | Human Fetal Heart                        | Uni-ZAP XR | LP03    |
| ННРВ ННРС ННРО ННРЕ ННРҒ<br>ННРG ННРН                        | Human Hippocampus                        | Uni-ZAP XR | LP03    |
| HCE1 HCE2 HCE3 HCE4 HCE5<br>HCEB HCEC HCED HCEE HCEF<br>HCEG | Human Cerebellum                         | Uni-ZAP XR | LP03    |
| HUVB HUVC HUVD HUVE                                          | Human Umbilical Vein, Endo.<br>remake    | Uni-ZAP XR | LP03    |
| HSTA HSTB HSTC HSTD                                          | Human Skin Tumor                         | Uni-ZAP XR | LP03    |
| HTAA HTAB HTAC HTAD HTAE                                     | Human Activated T-Cells                  | Uni-ZAP XR | LP03    |
| HFEA HFEB HFEC                                               | Human Fetal Epithelium (Skin)            | Uni-ZAP XR | LP03    |
| НЈРА НЈРВ НЈРС НЈРО                                          | HUMAN JURKAT MEMBRANE<br>BOUND POLYSOMES | Uni-ZAP XR | LP03    |
| HESA                                                         | Human epithelioid sarcoma                | Uni-Zap XR | LP03    |
| HLTA HLTB HLTC HLTD HLTE<br>HLTF                             | Human T-Cell Lymphoma                    | Uni-ZAP XR | LP03    |
| HFTA HFTB HFTC HFTD                                          | Human Fetal Dura Mater                   | Uni-ZAP XR | LP03    |
| HRDA HRDB HRDC HRDD<br>HRDE HRDF                             | Human Rhabdomyosarcoma                   | Uni-ZAP XR | LP03    |
| НСАА НСАВ НСАС                                               | Cem cells cyclohexamide treated          | Uni-ZAP XR | LP03    |
| HRGA HRGB HRGC HRGD                                          | Raji Cells, cyclohexamide treated        | Uni-ZAP XR | LP03    |
| HSUA HSUB HSUC HSUM                                          | Supt Cells, cyclohexamide treated        | Uni-ZAP XR | LP03    |
| HT4A HT4C HT4D                                               | Activated T-Cells, 12 hrs.               | Uni-ZAP XR | LP03    |
| НЕ9А НЕ9В НЕ9С НЕ9D НЕ9Е<br>НЕ9F НЕ9G НЕ9Н НЕ9М НЕ9N         | Nine Week Old Early Stage Human          | Uni-ZAP XR | LP03    |
| НАТА НАТВ НАТС НАТО НАТЕ                                     | Human Adrenal Gland Tumor                | Uni-ZAP XR | LP03    |
| HT5A                                                         | Activated T-Cells, 24 hrs.               | Uni-ZAP XR | LP03    |
| HFGA HFGM                                                    | Human Fetal Brain                        | Uni-ZAP XR | LP03    |
| HNEA HNEB HNEC HNED HNEE                                     | Human Neutrophil                         | Uni-ZAP XR | LP03    |
| HBGB HBGD                                                    | Human Primary Breast Cancer              | Uni-ZAP XR | LP03    |
| HBNA HBNB                                                    | Human Normal Breast                      | Uni-ZAP XR | LP03    |

| Libraries owned by Catalog                                   | Catalog Description                                            | Vector     | ATCC <sup>TM</sup><br>Deposit |
|--------------------------------------------------------------|----------------------------------------------------------------|------------|-------------------------------|
| HCAS                                                         | Cem Cells, cyclohexamide treated,<br>subtra                    | Uni-ZAP XR | LP03                          |
| HHPS                                                         | Human Hippocampus, subtracted                                  | pBS        | LP03                          |
| HKCS HKCU                                                    | Human Colon Cancer, subtracted                                 | pBS        | LP03                          |
| HRGS                                                         | Raji cells, cyclohexamide treated,<br>subtracted               | pBS        | LP03                          |
| HSUT                                                         | Supt cells, cyclohexamide treated,<br>differentially expressed | pBS        | LP03                          |
| HT4S                                                         | Activated T-Cells, 12 hrs,<br>subtracted                       | Uni-ZAP XR | LP03                          |
| HCDA HCDB HCDC HCDD<br>HCDE                                  | Human Chondrosarcoma                                           | Uni-ZAP XR | LP03                          |
| НОАА НОАВ НОАС                                               | Human Osteosarcoma                                             | Uni-ZAP XR | LP03                          |
| HTLA HTLB HTLC HTLD HTLE<br>HTLF                             | Human adult testis, large inserts                              | Uni-ZAP XR | LP03                          |
| HLMA HLMC HLMD                                               | Breast Lymph node cDNA library                                 | Uni-ZAP XR | LP03                          |
| Н6ЕА Н6ЕВ Н6ЕС                                               | HL-60, PMA 4H                                                  | Uni-ZAP XR | LP03                          |
| HTXA HTXB HTXC HTXD HTXE<br>HTXF HTXG HTXH                   | Activated T-Cell (12hs)/Thiouridine<br>labelledEco             | Uni-ZAP XR | LP03                          |
| HNFA HNFB HNFC HNFD HNFE<br>HNFF HNFG HNFH HNFJ              | Human Neutrophil, Activated                                    | Uni-ZAP XR | LP03                          |
| НТОВ НТОС                                                    | HUMAN TONSILS, FRACTION 2                                      | Uni-ZAP XR | LP03                          |
| HMGB                                                         | Human OB MG63 control fraction I                               | Uni-ZAP XR | LP03                          |
| HOPB                                                         | Human OB HOS control fraction I                                | Uni-ZAP XR | LP03                          |
| HORB                                                         | Human OB HOS treated (10 nM<br>E2) fraction I                  | Uni-ZAP XR | LP03                          |
| HSVA HSVB HSVC                                               | Human Chronic Synovitis                                        | Uni-ZAP XR | LP03                          |
| HROA                                                         | HUMAN STOMACH                                                  | Uni-ZAP XR | LP03                          |
| НВЈА НВЈВ НВЈС НВЈО НВЈЕ<br>НВЈГ НВЈС НВЈН НВЈІ НВЈЈ<br>НВЈК | HUMAN B CELL LYMPHOMA                                          | Uni-ZAP XR | LP03                          |
| HCRA HCRB HCRC                                               | human corpus colosum                                           | Uni-ZAP XR | LP03                          |
| HODA HODB HODC HODD                                          | human ovarian cancer                                           | Uni-ZAP XR | LP03                          |
| HDSA                                                         | Dermatofibrosarcoma Protuberance                               | Uni-ZAP XR | LP03                          |
| HMWA HMWB HMWC HMWD<br>HMWE HMWF HMWG HMWH<br>HMWI HMWJ      | Bone Marrow Cell Line (RS4;11)                                 | Uni-ZAP XR | LP03                          |
| HSOA                                                         | stomach cancer (human)                                         | Uni-ZAP XR | LP03                          |
| HERA                                                         | SKIN                                                           | Uni-ZAP XR | LP03                          |
| HMDA                                                         | Brain-medulloblastoma                                          | Uni-ZAP XR | LP03                          |
| HGLA HGLB HGLD                                               | Glioblastoma                                                   | Uni-ZAP XR | LP03                          |
| HEAA                                                         | H. Atrophic Endometrium                                        | Uni-ZAP XR | LP03                          |
| HBCA HBCB                                                    | H. Lymph node breast Cancer                                    | Uni-ZAP XR | LP03                          |
| HPWT                                                         | Human Prostate BPH, re-excision                                | Uni-ZAP XR | LP03                          |
| HFVG HFVH HFVI                                               | Fetal Liver, subtraction II                                    | pBS        | LP03                          |
| HNFI                                                         | Human Neutrophils, Activated, re-<br>excision                  | pBS        | LP03                          |
| НВМВ НВМС НВМО                                               | Human Bone Marrow, re-excision                                 | pBS        | LP03                          |
| HKML HKMM HKMN                                               | H. Kidney Medulla, re-excision                                 | pBS        | LP03                          |
| HKIX HKIY                                                    | H. Kidney Cortex, subtracted                                   | pBS        | LP03                          |
| HADT                                                         | H. Amygdala Depression,<br>subtracted                          | pBS        | LP03                          |

| Libraries owned by Catalog                                   | Catalog Description                                | Vector     | ATCC <sup>TM</sup><br>Deposit |
|--------------------------------------------------------------|----------------------------------------------------|------------|-------------------------------|
| H6AS                                                         | HI-60, untreated, subtracted                       | Uni-ZAP XR | LP03                          |
| H6ES                                                         | HL-60, PMA 4H, subtracted                          | Uni-ZAP XR | LP03                          |
| 16BS                                                         | HL-60, RA 4h, Subtracted                           | Uni-ZAP XR | LP03                          |
| H6CS                                                         | HL-60, PMA 1d, subtracted                          | Uni-ZAP XR | LP03                          |
| HTXJ HTXK                                                    | Activated T-cell(12h)/Thiouridine-<br>re-excision  | Uni-ZAP XR | LP03                          |
| HMSA HMSB HMSC HMSD<br>HMSE HMSF HMSG HMSH HMSI<br>HMSJ HMSK | Monocyte activated                                 | Uni-ZAP XR | LP03                          |
| HAGA HAGB HAGC HAGD<br>HAGE HAGF                             | Human Amygdala                                     | Uni-ZAP XR | LP03                          |
| HSRA HSRB HSRE                                               | STROMAL -OSTEOCLASTOMA                             | Uni-ZAP XR | LP03                          |
| HSRD HSRF HSRG HSRH                                          | Human Osteoclastoma Stromal<br>Cells - unamplified | Uni-ZAP XR | LP03                          |
| HSQA HSQB HSQC HSQD HSQE<br>HSQF HSQG                        | Stromal cell TF274                                 | Uni-ZAP XR | LP03                          |
| HSKA HSKB HSKC HSKD HSKE<br>HSKF HSKZ                        | Smooth muscle, serum treated                       | Uni-ZAP XR | LP03                          |
| HSLA HSLB HSLC HSLD HSLE<br>HSLF HSLG                        | Smooth muscle,control                              | Uni-ZAP XR | LP03                          |
| HSDA HSDD HSDE HSDF HSDG<br>HSDH                             | Spinal cord                                        | Uni-ZAP XR | LP03                          |
| HPWS                                                         | Prostate-BPH subtracted II                         | pBS        | LP03                          |
| ISKW HSKX HSKY                                               | Smooth Muscle- HASTE<br>normalized                 | pBS        | LP03                          |
| HFPB HFPC HFPD                                               | H. Frontal cortex,epileptic;re-<br>excision        | Uni-ZAP XR | LP03                          |
| HSDI HSDJ HSDK                                               | Spinal Cord, re-excision                           | Uni-ZAP XR | LP03                          |
| ISKN HSKO                                                    | Smooth Muscle Serum Treated,<br>Norm               | pBS        | LP03                          |
| HSKG HSKH HSKI                                               | Smooth muscle, serum induced,re-<br>exc            | pBS        | LP03                          |
| HFCA HFCB HFCC HFCD HFCE<br>HFCF                             | Human Fetal Brain                                  | Uni-ZAP XR | LP04                          |
| HPTA HPTB HPTD                                               | Human Pituitary                                    | Uni-ZAP XR | LP04                          |
| НТНВ НТНС НТНО                                               | Human Thymus                                       | Uni-ZAP XR | LP04                          |
| HE6B HE6C HE6D HE6E HE6F<br>HE6G HE6S                        | Human Whole Six Week Old<br>Embryo                 | Uni-ZAP XR | LP04                          |
| HSSA HSSB HSSC HSSD HSSE<br>HSSF HSSG HSSH HSSI HSSJ<br>HSSK | Human Synovial Sarcoma                             | Uni-ZAP XR | LP04                          |
| HE7T                                                         | 7 Week Old Early Stage Human,<br>subtracted        | Uni-ZAP XR | LP04                          |
| ЕРА НЕРВ НЕРС                                                | Human Epididymus                                   | Uni-ZAP XR | LP04                          |
| ISNA HSNB HSNC HSNM HSNN                                     |                                                    | Uni-ZAP XR | LP04                          |
| IPFB HPFC HPFD HPFE                                          | Human Prostate Cancer, Stage C<br>fraction         | Uni-ZAP XR | LP04                          |
| HE2A HE2D HE2E HE2H HE2I<br>HE2M HE2N HE2O                   | 12 Week Old Early Stage Human                      | Uni-ZAP XR | LP04                          |
| HE2B HE2C HE2F HE2G HE2P<br>HE2Q                             | 12 Week Old Early Stage Human, II                  |            | LP04                          |
| HPTS HPTT HPTU                                               | Human Pituitary, subtracted                        | Uni-ZAP XR | LP04                          |
| HAUA HAUB HAUC                                               | Amniotic Cells - TNF induced                       | Uni-ZAP XR | LP04                          |
| HAQA HAQB HAQC HAQD                                          | Amniotic Cells - Primary Culture                   | Uni-ZAP XR | LP04                          |

| Libraries owned by Catalog                              | Catalog Description                           | Vector     | АТССТМ  |
|---------------------------------------------------------|-----------------------------------------------|------------|---------|
| Distances owned by Canada                               | Cutatog Description                           | , color    | Deposit |
| HWTA HWTB HWTC                                          | wilm's tumor                                  | Uni-ZAP XR | LP04    |
| HBSD                                                    | Bone Cancer, re-excision                      | Uni-ZAP XR | LP04    |
| HSGB                                                    | Salivary gland, re-excision                   | Uni-ZAP XR | LP04    |
| HSJA HSJB HSJC                                          | Smooth muscle-ILb induced                     | Uni-ZAP XR | LP04    |
| HSXA HSXB HSXC HSXD                                     | Human Substantia Nigra                        | Uni-ZAP XR | LP04    |
| HSHA HSHB HSHC                                          | Smooth muscle, IL1b induced                   | Uni-ZAP XR | LP04    |
| HOUA HOUB HOUC HOUD                                     | Adipocytes                                    | Uni-ZAP XR | LP04    |
| HPWA HPWB HPWC HPWD<br>HPWE                             | Prostate BPH                                  | Uni-ZAP XR | LP04    |
| HELA HELB HELC HELD HELE<br>HELF HELG HELH              | Endothelial cells-control                     | Uni-ZAP XR | LP04    |
| HEMA HEMB HEMC HEMD<br>HEME HEMF HEMG HEMH              | Endothelial-induced                           | Uni-ZAP XR | LP04    |
| HBIA HBIB HBIC                                          | Human Brain, Striatum                         | Uni-ZAP XR | LP04    |
| HHSA HHSB HHSC HHSD HHSE                                | Human Hypothalmus, Schizophrenia              | Uni-ZAP XR | LP04    |
| HNGA HNGB HNGC HNGD<br>HNGE HNGF HNGG HNGH HNGI<br>HNGJ | neutrophils control                           | Uni-ZAP XR | LP04    |
| HNHA HNHB HNHC HNHD<br>HNHE HNHF HNHG HNHH HNHI<br>HNHJ |                                               | Uni-ZAP XR | LP04    |
| HSDB HSDC                                               | STRIATUM DEPRESSION                           | Uni-ZAP XR | LP04    |
| HHPT                                                    | Hypothalamus                                  | Uni-ZAP XR | LP04    |
| HSAT HSAU HSAV HSAW HSAX<br>HSAY HSAZ                   |                                               | Uni-ZAP XR | LP04    |
| HBMS HBMT HBMU HBMV<br>HBMW HBMX                        | Bone marrow                                   | Uni-ZAP XR | LP04    |
| HOEA HOEB HOEC HOED HOEE<br>HOEF HOEJ                   |                                               | Uni-ZAP XR | LP04    |
| HAIA HAIB HAIC HAID HAIE<br>HAIF                        | Epithelial-TNFa and INF induced               | Uni-ZAP XR | LP04    |
| HTGA HTGB HTGC HTGD                                     | Apoptotic T-cell                              | Uni-ZAP XR | LP04    |
| HMCA HMCB HMCC HMCD<br>HMCE                             | Macrophage-oxLDL                              | Uni-ZAP XR | LP04    |
| HMAA HMAB HMAC HMAD<br>HMAE HMAF HMAG                   | Macrophage (GM-CSF treated)                   | Uni-ZAP XR | LP04    |
| НРНА                                                    | Normal Prostate                               | Uni-ZAP XR | LP04    |
| НРІА НРІВ НРІС                                          | LNCAP prostate cell line                      | Uni-ZAP XR | LP04    |
| НРЈА НРЈВ НРЈС                                          | PC3 Prostate cell line                        | Uni-ZAP XR | LP04    |
| HOSE HOSF HOSG                                          | Human Osteoclastoma, re-excision              | Uni-ZAP XR | LP04    |
| HTGE HTGF                                               | Apoptotic T-cell, re-excision                 | Uni-ZAP XR | LP04    |
| HMAJ HMAK                                               | H Macrophage (GM-CSF treated),<br>re-excision | Uni-ZAP XR | LP04    |
| HACB HACC HACD                                          | Human Adipose Tissue, re-excision             | Uni-ZAP XR | LP04    |
| HFPA                                                    | H. Frontal Cortex, Epileptic                  | Uni-ZAP XR | LP04    |
| HFAA HFAB HFAC HFAD HFAE                                | Alzheimer's, spongy change                    | Uni-ZAP XR | LP04    |
| HFAM                                                    | Frontal Lobe, Dementia                        | Uni-ZAP XR | LP04    |
| HMIA HMIB HMIC                                          | Human Manic Depression Tissue                 | Uni-ZAP XR | LP04    |
| HTSA HTSE HTSF HTSG HTSH                                | Human Thymus                                  | pBS        | LP05    |
|                                                         |                                               | ·          |         |
| HPBA HPBB HPBC HPBD HPBE                                | Human Pineal Gland                            | pBS        | LP05    |

| Libraries owned by Catalog  | Catalog Description                                           | Vector         | ATCCTM  |
|-----------------------------|---------------------------------------------------------------|----------------|---------|
|                             |                                                               |                | Deposit |
| HSBA HSBB HSBC HSBM         | HSC172 cells                                                  | pBS            | LP05    |
| НЈАА НЈАВ НЈАС НЈАД         | Jurkat T-cell G1 phase                                        | pBS            | LP05    |
| HJBA HJBB HJBC HJBD         | Jurkat T-Cell, S phase                                        | pBS            | LP05    |
| HAFA HAFB                   | Aorta endothelial cells + TNF-a                               | pBS            | LP05    |
| HAWA HAWB HAWC              | Human White Adipose                                           | pBS            | LP05    |
| HTNA HTNB                   | Human Thyroid                                                 | pBS            | LP05    |
| HONA                        | Normal Ovary, Premenopausal                                   | pBS            | LP05    |
| HARA HARB                   | Human Adult Retina                                            | pBS            | LP05    |
| HLJA HLJB                   | Human Lung                                                    | pCMVSport 1    | LP06    |
| HOFM HOFN HOFO              | H. Ovarian Tumor, II, OV5232                                  | pCMVSport 2.0  | LP07    |
| HOGA HOGB HOGC              | OV 10-3-95                                                    | pCMVSport 2.0  | LP07    |
| HCGL                        | CD34+cells, II                                                | pCMVSport 2.0  | LP07    |
| HDLA                        | Hodgkin's Lymphoma I                                          | pCMVSport 2.0  | LP07    |
| HDTA HDTB HDTC HDTD HDTE    | Hodgkin's Lymphoma II                                         | pCMVSport 2.0  | LP07    |
| HKAA HKAB HKAC HKAD         | Keratinocyte                                                  | pCMVSport2.0   | LP07    |
| HKAE HKAF HKAG HKAH         | Terumocy te                                                   | pent roporta.o | Li o,   |
| HCIM                        | CAPFINDER, Crohn's Disease, lib<br>2                          | pCMVSport 2.0  | LP07    |
| HKAL                        | Keratinocyte, lib 2                                           | pCMVSport2.0   | LP07    |
| HKAT                        | Keratinocyte, lib 3                                           | pCMVSport2.0   | LP07    |
| HNDA                        | Nasal polyps                                                  | pCMVSport2.0   | LP07    |
| HDRA                        | H. Primary Dendritic Cells lib 3                              | pCMVSport2.0   | LP07    |
| НОНА НОНВ НОНС              | Human Osteoblasts II                                          | pCMVSport2.0   | LP07    |
| HLDA HLDB HLDC              | Liver, Hepatoma                                               | pCMVSport3.0   | LP08    |
| HLDN HLDO HLDP              | Human Liver, normal                                           | pCMVSport3.0   | LP08    |
| HMTA                        | pBMC stimulated w/ poly I/C                                   | pCMVSport3.0   | LP08    |
| HNTA                        | NTERA2, control                                               | pCMVSport3.0   | LP08    |
| HDPA HDPB HDPC HDPD HDPF    | Primary Dendritic Cells, lib 1                                | pCMVSport3.0   | LP08    |
| HDPG HDPH HDPI HDPJ HDPK    | Timming Benarius Centr, no 1                                  | peni i sporo.  | 21 00   |
| HDPM HDPN HDPO HDPP         | Primary Dendritic cells,frac 2                                | pCMVSport3.0   | LP08    |
| HMUA HMUB HMUC              | Myoloid Progenitor Cell Line                                  | pCMVSport3.0   | LP08    |
| HHEA HHEB HHEC HHED         | T Cell helper I                                               | pCMVSport3.0   | LP08    |
| HHEM HHEN HHEO HHEP         | T cell helper II                                              | pCMVSport3.0   | LP08    |
| HEQA HEQB HEQC              | Human endometrial stromal cells                               | pCMVSport3.0   | LP08    |
| НІМА НІМВ                   | Human endometrial stromal cells-<br>treated with progesterone | pCMVSport3.0   | LP08    |
| HSWA HSWB HSWC              | Human endometrial stromal cells-<br>treated with estradiol    | pCMVSport3.0   | LP08    |
| HSYA HSYB HSYC              | Human Thymus Stromal Cells                                    | pCMVSport3.0   | LP08    |
| HLWA HLWB HLWC              | Human Placenta                                                | pCMVSport3.0   | LP08    |
| HRAA HRAB H <b>RA</b> C     | Rejected Kidney, lib 4                                        | pCMVSport3.0   | LP08    |
| HMTM                        | PCR, pBMC I/C treated                                         | PCRII          | LP09    |
| НМЈА                        | H. Meniingima, M6                                             | pSport 1       | LP10    |
| НМКА НМКВ НМКС НМКD<br>НМКЕ | H. Meningima, M1                                              | pSport 1       | LP10    |
| HUSG HUSI                   | Human umbilical vein endothelial cells, IL-4 induced          | pSport 1       | LP10    |
| HUSX HUSY                   | Human Umbilical Vein Endothelial<br>Cells, uninduced          | pSport 1       | LP10    |
| HOFA                        | Ovarian Tumor I, OV5232                                       | pSport 1       | LP10    |

| Libraries owned by Catalog  | Catalog Description                                              | Vector   | ATCCTM          |
|-----------------------------|------------------------------------------------------------------|----------|-----------------|
| HCFA HCFB HCFC HCFD         | T-Cell PHA 16 hrs                                                | pSport 1 | Deposit<br>LP10 |
| HCFL HCFM HCFN HCFO         | T-Cell PHA 24 hrs                                                | pSport 1 | LP10            |
| HADA HADC HADD HADE         | Human Adipose                                                    | pSport 1 | LP10            |
| HADF HADG                   | ·                                                                |          |                 |
| HOVA HOVB HOVC              | Human Ovary                                                      | pSport 1 | LP10            |
| HTWB HTWC HTWD HTWE<br>HTWF | Resting T-Cell Library,II                                        | pSport 1 | LP10            |
| НММА                        | Spleen metastic melanoma                                         | pSport 1 | LP10            |
| HLYA HLYB HLYC HLYD HLYI    | leukemia                                                         | pSport 1 | LP10            |
| HCGA                        | CD34+ cell, I                                                    | pSport 1 | LP10            |
| HEOM HEON                   | Human Eosinophils                                                | pSport 1 | LP10            |
| HTDA                        | Human Tonsil, Lib 3                                              | pSport 1 | LP10            |
| HSPA                        | Salivary Gland, Lib 2                                            | pSport 1 | LP10            |
| НСНА НСНВ НСНС              | Breast Cancer cell line, MDA 36                                  | pSport 1 | LP10            |
| HCHM HCHN                   | Breast Cancer Cell line, angiogenic                              | pSport 1 | LP10            |
| HCIA                        | Crohn's Disease                                                  | pSport 1 | LP10            |
| HDAA HDAB HDAC              | HEL cell line                                                    | pSport 1 | LP10            |
| HABA                        | Human Astrocyte                                                  | pSport 1 | LP10            |
| HUFA HUFB HUFC              | Ulcerative Colitis                                               | pSport 1 | LP10            |
| HNTM                        | NTERA2 + retinoic acid, 14 days                                  | pSport 1 | LP10            |
| HDQA                        | Primary Dendritic cells, CapFinder2,<br>frac 1                   | pSport 1 | LP10            |
| HDQM                        | Primary Dendritic Cells, CapFinder,<br>frac 2                    | pSport 1 | LP10            |
| HLDX                        | Human Liver, normal,CapFinder                                    | pSport 1 | LP10            |
| HULA HULB HULC              | Human Dermal Endothelial<br>Cells,untreated                      | pSport1  | LP10            |
| HUMA                        | Human Dermal Endothelial<br>cells.treated                        | pSport1  | LP10            |
| НСЈА                        | Human Stromal Endometrial<br>fibroblasts, untreated              | pSport1  | LP10            |
| НСЈМ                        | Human Stromal endometrial<br>fibroblasts, treated w/ estradiol   | pSport1  | LP10            |
| HEDA                        | Human Stromal endometrial fibroblasts, treated with progesterone | pSport1  | LP10            |
| HFNA                        | Human ovary tumor cell OV350721                                  | pSport1  | LP10            |
| HKGA HKGB HKGC HKGD         | Merkel Cells                                                     | pSport1  | LP10            |
| HISA HISB HISC              | Pancreas Islet Cell Tumor                                        | pSport1  | LP10            |
| HLSA                        | Skin, burned                                                     | pSportl  | LP10            |
| HBZA                        | Prostate,BPH, Lib 2                                              | pSport 1 | LP10            |
| HBZS                        | Prostate BPH,Lib 2, subtracted                                   | pSport 1 | LP10            |
| HFIA HFIB HFIC              | Synovial Fibroblasts (control)                                   | pSport 1 | LP10            |
| НЕІН НЕП НЕП                | Synovial hypoxia                                                 | pSport 1 | LP10            |
| HFIT HFIU HFIV              | Synovial IL-1/TNF stimulated                                     | pSport 1 | LP10            |
| HGCA                        | Messangial cell, frac 1                                          | pSport1  | LP10            |
| HMVA HMVB HMVC              | Bone Marrow Stromal Cell,                                        | pSport1  | LP10            |
| HFIX HFIY HFIZ              | Synovial Fibroblasts (III/TNF), subt                             | pSport1  | LP10            |
| HFOX HFOY HFOZ              | Synovial hypoxia-RSF subtracted                                  | pSport1  | LP10            |

| Libraries owned by Catalog  | Catalog Description                               | Vector        | ATCC <sup>TM</sup> |
|-----------------------------|---------------------------------------------------|---------------|--------------------|
| HMQA HMQB HMQC HMQD         | Human Activated Monocytes                         | Uni-ZAP XR    | Deposit<br>LP11    |
| HLIA HLIB HLIC              | Human Liver                                       | pCMVSport 1   | LP012              |
| HHBA HHBB HHBC HHBD         | Human Heart                                       | pCMVSport 1   | LP012              |
| ННВЕ                        |                                                   | p, op         |                    |
| НВВА НВВВ                   | Human Brain                                       | pCMVSport 1   | LP012              |
| HLJA HLJB HLJC HLJD HLJE    | Human Lung                                        | pCMVSport 1   | LP012              |
| HOGA HOGB HOGC              | Ovarian Tumor                                     | pCMVSport 2.0 | LP012              |
| HTJM                        | Human Tonsils, Lib 2                              | pCMVSport 2.0 | LP012              |
| HAMF HAMG                   | KMH2                                              | pCMVSport 3.0 | LP012              |
| НАЈА НАЈВ НАЈС              | L428                                              | pCMVSport 3.0 | LP012              |
| HWBA HWBB HWBC HWBD<br>HWBE | Dendritic cells, pooled                           | pCMVSport 3.0 | LP012              |
| HWAA HWAB HWAC HWAD<br>HWAE | Human Bone Marrow, treated                        | pCMVSport 3.0 | LP012              |
| НҮАА НҮАВ НҮАС              | B Cell lymphoma                                   | pCMVSport 3.0 | LP012              |
| HWHG HWHH HWHI              | Healing groin wound, 6.5 hours post<br>incision   |               | LP012              |
| HWHP HWHQ HWHR              | Healing groin wound; 7.5 hours                    | pCMVSport 3.0 | LP012              |
| HARM                        |                                                   | pCMVSport 3.0 | LP012              |
| HBIM                        | Olfactory epithelium; nasalcavity                 | pCMVSport 3.0 | LP012              |
| HWDA                        | Healing Abdomen wound; 70&90<br>min post incision | pCMVSport 3.0 | LP012              |
| HWEA                        | Healing Abdomen Wound;15 days<br>post incision    | pCMVSport 3.0 | LP012              |
| HWJA                        | Healing Abdomen Wound;21&29<br>days               | pCMVSport 3.0 | LP012              |
| HNAL                        | Human Tongue, frac 2                              | pSport1       | LP012              |
| НМЈА                        | H. Meniingima, M6                                 | pSport1       | LP012              |
| HMKA HMKB HMKC HMKD<br>HMKE | H. Meningima, M1                                  | pSport1       | LP012              |
| HOFA                        | Ovarian Tumor I, OV5232                           | pSport1       | LP012              |
| HCFA HCFB HCFC HCFD         | T-Cell PHA 16 hrs                                 | pSport1       | LP012              |
| HCFL HCFM HCFN HCFO         | T-Cell PHA 24 hrs                                 | pSport1       | LP012              |
| HMMA HMMB HMMC              | Spleen metastic melanoma                          | pSport1       | LP012              |
| HTDA                        | Human Tonsil, Lib 3                               | pSport1       | LP012              |
| HDBA                        | Human Fetal Thymus                                | pSport1       | LP012              |
| HDUA                        | Pericardium                                       | pSport1       | LP012              |
| HBZA                        | Prostate,BPH, Lib 2                               | pSport1       | LP012              |
| HWCA                        | Larynx tumor                                      | pSport1       | LP012              |
| HWKA                        | Normal lung                                       | pSport1       | LP012              |
| HSMB                        | Bone marrow stroma,treated                        | pSport1       | LP012              |
| НВНМ                        | Normal trachea                                    | pSport1       | LP012              |
| HLFC                        | Human Larynx                                      | pSport1       | LP012              |
| HLRB                        | Siebben Polyposis                                 | pSport1       | LP012              |
| HNIA                        | Mammary Gland                                     | pSport1       | LP012              |
| HNJB                        | Palate carcinoma                                  | pSport1       | LP012              |
| HNKA                        | Palate normal                                     | pSport1       | LP012              |
| HMZA                        | Pharynx carcinoma                                 | pSport1       | LP012              |
| HABG                        | Cheek Carcinoma                                   | pSport1       | LP012              |
| HMZM                        | Pharynx Carcinoma                                 | pSport1       | LP012              |
| HDRM                        | Larynx Carcinoma                                  | pSport1       | LP012              |
| HVAA                        | Pancreas normal PCA4 No                           | pSport1       | LP012              |

| Libraries owned by Catalog  | Catalog Description                                            | Vector          | ATCC <sup>TM</sup><br>Deposit |
|-----------------------------|----------------------------------------------------------------|-----------------|-------------------------------|
| HICA                        | Tongue carcinoma                                               | pSport1         | LP012                         |
| HUKA HUKB HUKC HUKD<br>HUKE | Human Uterine Cancer                                           | Lambda ZAP II   | LP013                         |
| HFFA                        | Human Fetal Brain, random primed                               | Lambda ZAP II   | LP013                         |
| HTUA                        | Activated T-cell labeled with 4-<br>thioluri                   | Lambda ZAP II   | LP013                         |
| HBQA                        | Early Stage Human Brain, random<br>primed                      | Lambda ZAP II   | LP013                         |
| НМЕВ                        | Human microvascular Endothelial<br>cells, fract. B             | Lambda ZAP II   | LP013                         |
| HUSH                        | cells, fract. A, re-excision                                   | Lambda ZAP II   | LP013                         |
| HLQC HLQD                   | Hepatocellular tumor, re-excision                              | Lambda ZAP II   | LP013                         |
| HTWJ HTWK HTWL              | Resting T-cell, re-excision                                    | Lambda ZAP II   | LP013                         |
| HF6S                        | Human Whole 6 week Old Embryo<br>(II), subt                    | pBluescript     | LP013                         |
| HHPS                        | Human Hippocampus, subtracted                                  | pBluescript     | LP013                         |
| HL1S                        | LNCAP, differential expression                                 | pBluescript     | LP013                         |
| HLHS HLHT                   | Early Stage Human Lung,<br>Subtracted                          | pBluescript     | LP013                         |
| HSUS                        | Supt cells, cyclohexamide treated,<br>subtracted               | pBluescript     | LP013                         |
| HSUT                        | Supt cells, cyclohexamide treated,<br>differentially expressed | pBluescript     | LP013                         |
| HSDS                        | H. Striatum Depression, subtracted                             | pBluescript     | LP013                         |
| IPTZ                        | Human Pituitary, Subtracted VII                                | pBluescript     | LP013                         |
| HSDX                        | H. Striatum Depression, subt II                                | pBluescript     | LP013                         |
| HSDZ                        | H. Striatum Depression, subt                                   | pBluescript     | LP013                         |
| HPBA HPBB HPBC HPBD HPBE    | Human Pincal Gland                                             | pBluescript SK- | LP013                         |
| IRTA                        | Colorectal Tumor                                               | pBluescript SK- | LP013                         |
| HSBA HSBB HSBC HSBM         | HSC172 cells                                                   | pBluescript SK- | LP013                         |
| НЈАА НЈАВ НЈАС НЈАД         | Jurkat T-cell G1 phase                                         | pBluescript SK- | LP013                         |
| НЈВА НЈВВ НЈВС НЈВО         | Jurkat T-cell, S1 phase                                        | pBluescript SK- | LP013                         |
| HTNA HTNB                   | Human Thyroid                                                  | pBluescript SK- | LP013                         |
| НАНА НАНВ                   | Human Adult Heart                                              | Uni-ZAP XR      | LP013                         |
| HE6A                        | Whole 6 week Old Embryo                                        | Uni-ZAP XR      | LP013                         |
| HFCA HFCB HFCC HFCD HFCE    | Human Fetal Brain                                              | Uni-ZAP XR      | LP013                         |
| HFKC HFKD HFKE HFKF HFKG    | Human Fetal Kidney                                             | Uni-ZAP XR      | LP013                         |
| HGBA HGBD HGBE HGBF<br>HGBG | Human Gall Bladder                                             | Uni-ZAP XR      | LP013                         |
| HPRA HPRB HPRC HPRD         | Human Prostate                                                 | Uni-ZAP XR      | LP013                         |
| HTEA HTEB HTEC HTED HTEE    | Human Testes                                                   | Uni-ZAP XR      | LP013                         |
| HTTA HTTB HTTC HTTD HTTE    | Human Testes Tumor                                             | Uni-ZAP XR      | LP013                         |
| НҮВА НҮВВ                   | Human Fetal Bone                                               | Uni-ZAP XR      | LP013                         |
| HFLA                        | Human Fetal Liver                                              | Uni-ZAP XR      | LP013                         |
| HIFB HHFC HHFD HHFE HHFF    | Human Fetal Heart                                              | Uni-ZAP XR      | LP013                         |
| HUVB HUVC HUVD HUVE         | Human Umbilical Vein, End.<br>remake                           | Uni-ZAP XR      | LP013                         |
| НТНВ НТНС НТНО              | Human Thymus                                                   | Uni-ZAP XR      | LP013                         |
| HSTA HSTB HSTC HSTD         | Human Skin Tumor                                               | Uni-ZAP XR      | LP013                         |
| HTAA HTAB HTAC HTAD HTAE    | Human Activated T-cells                                        | Uni-ZAP XR      | LP013                         |
| HFEA HFEB HFEC              | Human Fetal Epithelium (skin)                                  | Uni-ZAP XR      | LP013                         |
| НЈРА НЈРВ НЈРС НЈРО         | Human Jurkat Membrane Bound<br>Polysomes                       | Uni-ZAP XR      | LP013                         |

| Libraries owned by Catalog  | Catalog Description                          | Vector      | ATCC <sup>TM</sup> |
|-----------------------------|----------------------------------------------|-------------|--------------------|
| Elitaties owned by Catalog  | Catalog Description                          | VCCIOI      | Deposit            |
| HESA                        | Human Epithelioid Sarcoma                    | Uni-ZAP XR  | LP013              |
| HALS                        | Human Adult Liver, Subtracted                | Uni-ZAP XR  | LP013              |
| HFTA HFTB HFTC HFTD         | Human Fetal Dura Mater                       | Uni-ZAP XR  | LP013              |
| HCAA HCAB HCAC              | Cem cells, cyclohexamide treated             | Uni-ZAP XR  | LP013              |
| HRGA HRGB HRGC HRGD         | Raji Cells, cyclohexamide treated            | Uni-ZAP XR  | LP013              |
| НЕ9А НЕ9В НЕ9С НЕ9В НЕ9Е    | Nine Week Old Early Stage Human              | Uni-ZAP XR  | LP013              |
| HSFA                        | Human Fibrosarcoma                           | Uni-ZAP XR  | LP013              |
| HATA HATB HATC HATD HATE    |                                              | Uni-ZAP XR  | LP013              |
| HTRA                        | Human Trachea Tumor                          | Uni-ZAP XR  | LP013              |
| HE2A HE2D HE2E HE2H HE2I    | 12 Week Old Early Stage Human                | Uni-ZAP XR  | LP013              |
| HE2B HE2C HE2F HE2G HE2P    | 12 Week Old Early Stage Human, II            | Uni-ZAP XR  | LP013              |
| HNEA HNEB HNEC HNED HNEE    |                                              | Uni-ZAP XR  | LP013              |
| HBGA                        | Human Primary Breast Cancer                  | Uni-ZAP XR  | LP013              |
| HPTS HPTT HPTU              | Human Pituitary, subtracted                  | Uni-ZAP XR  | LP013              |
| HMQA HMQB HMQC HMQD         | Human Activated Monocytes                    | Uni-ZAP XR  | LP013              |
| HOAA HOAB HOAC              | Human Osteosarcoma                           | Uni-ZAP XR  | LP013              |
|                             |                                              |             |                    |
| HTOA HTOD HTOE HTOF HTOG    | human tonsils                                | Uni-ZAP XR  | LP013              |
| HMGB                        | Human OB MG63 control fraction I             |             | LP013              |
| HOPB                        | Human OB HOS control fraction I              | Uni-ZAP XR  | LP013              |
| HOQB                        | Human OB HOS treated (1 nM E2)<br>fraction I | Uni-ZAP XR  | LP013              |
| HAUA HAUB HAUC              | Amniotic Cells - TNF induced                 | Uni-ZAP XR  | LP013              |
| HAQA HAQB HAQC HAQD         | Amniotic Cells - Primary Culture             | Uni-ZAP XR  | LP013              |
| HROA HROC                   | HUMAN STOMACH                                | Uni-ZAP XR  | LP013              |
| НВЈА НВЈВ НВЈС НВЈО НВЈЕ    | HUMAN B CELL LYMPHOMA                        | Uni-ZAP XR  | LP013              |
| HODA HODB HODC HODD         | human ovarian cancer                         | Uni-ZAP XR  | LP013              |
| HCPA                        | Corpus Callosum                              | Uni-ZAP XR  | LP013              |
| HSOA                        | stomach cancer (human)                       | Uni-ZAP XR  | LP013              |
| HERA                        | SKIN                                         | Uni-ZAP XR  | LP013              |
| HMDA                        | Brain-medulloblastoma                        | Uni-ZAP XR  | LP013              |
| HGLA HGLB HGLD              | Glioblastoma                                 | Uni-ZAP XR  | LP013              |
| HWTA HWTB HWTC              | wilm's tumor                                 | Uni-ZAP XR  | LP013              |
| HEAA                        | H. Atrophic Endometrium                      | Uni-ZAP XR  | LP013              |
| HAPN HAPO HAPP HAPQ HAPR    | Human Adult Pulmonary;re-<br>excision        | Uni-ZAP XR  | LP013              |
| HLTG HLTH                   | Human T-cell lymphoma;re-<br>excision        | Uni-ZAP XR  | LP013              |
| HAHC HAHD HAHE              | Human Adult Heart;re-excision                | Uni-ZAP XR  | LP013              |
| HAGA HAGB HAGC HAGD<br>HAGE | Human Amygdala                               | Uni-ZAP XR  | LP013              |
| HSJA HSJB HSJC              | Smooth muscle-ILb induced                    | Uni-ZAP XR  | LP013              |
| HSHA HSHB HSHC              | Smooth muscle, IL1b induced                  | Uni-ZAP XR  | LP013              |
| HPWA HPWB HPWC HPWD         | Prostate BPH                                 | Uni-ZAP XR  | LP013              |
| HPWE                        | I IOSIAIC DI II                              | UIII-ZAI AK | LI 013             |
| HPIA HPIB HPIC              | LNCAP prostate cell line                     | Uni-ZAP XR  | LP013              |
| НРЈА НРЈВ НРЈС              | PC3 Prostate cell line                       | Uni-ZAP XR  | LP013              |
| НВТА                        | Bone Marrow Stroma, TNF&LPS                  | Uni-ZAP XR  | LP013              |
| HMCF HMCG HMCH HMCI<br>HMCJ | Macrophage-oxLDL; re-excision                | Uni-ZAP XR  | LP013              |
| HAGG HAGH HAGI              | Human Amygdala;re-excision                   | Uni-ZAP XR  | LP013              |
| HACA                        | H. Adipose Tissue                            | Uni-ZAP XR  | LP013              |
| HKFB                        | K562 + PMA (36 hrs),re-excision              | ZAP Express | LP013              |
| шкго                        | ESOS : CIVIA (50 IIIS), re-excision          | ZAI EXPIESS | L1013              |

| Libraries owned by Catalog | Catalog Description                        | Vector        | ATCC <sup>TM</sup><br>Deposit |
|----------------------------|--------------------------------------------|---------------|-------------------------------|
| HCWT HCWU HCWV             | CD34 positive cells (cord blood),re-<br>ex | ZAP Express   | LP013                         |
| HBWA                       | Whole brain                                | ZAP Express   | LP013                         |
| HBXA HBXB HBXC HBXD        | Human Whole Brain #2 - Oligo dT<br>> 1.5Kb | ZAP Express   | LP013                         |
| HAVM                       | Temporal cortex-Alzheizmer                 | pT-Adv        | LP014                         |
| HAVT                       | Hippocampus, Alzheimer<br>Subtracted       | pT-Adv        | LP014                         |
| HHAS                       | CHME Cell Line                             | Uni-ZAP XR    | LP014                         |
| HAJR                       | Larynx normal                              | pSport 1      | LP014                         |
| HWLE HWLF HWLG HWLH        | Colon Normal                               | pSport 1      | LP014                         |
| HCRM HCRN HCRO             | Colon Carcinoma                            | pSport 1      | LP014                         |
| HWLI HWLJ HWLK             | Colon Normal                               | pSport 1      | LP014                         |
| HWLQ HWLR HWLS HWLT        | Colon Tumor                                | pSport 1      | LP014                         |
| IBFM                       | Gastrocnemius Muscle                       | pSport 1      | LP014                         |
| HBOD HBOE                  | Quadriceps Muscle                          | pSport 1      | LP014                         |
| HBKD HBKE                  | Soleus Muscle                              | pSport 1      | LP014                         |
| HCCM                       | Pancreatic Langerhans                      | pSport 1      | LP014                         |
| HWGA                       | Larynx carcinoma                           | pSport 1      | LP014                         |
| HWGM HWGN                  | Larynx carcinoma                           | pSport 1      | LP014                         |
| HWLA HWLB HWLC             | Normal colon                               | pSport 1      | LP014                         |
| HWLM HWLN                  | Colon Tumor                                | pSport 1      | LP014                         |
| HVAM HVAN HVAO             | Pancreas Tumor                             | pSport 1      | LP014                         |
| HWGQ                       | Larynx carcinoma                           | pSport 1      | LP014                         |
| HAQM HAQN                  | Salivary Gland                             | pSport 1      | LP014                         |
| HASM                       | Stomach; normal                            | pSport 1      | LP014                         |
| HBCM                       | Uterus; normal                             | pSport 1      | LP014                         |
| HCDM                       | Testis; normal                             | pSport 1      | LP014                         |
| HDJM                       | Brain; normal                              | pSport 1      | LP014                         |
| HEFM                       | Adrenal Gland,normal                       | pSport 1      | LP014                         |
| HBAA                       | Rectum normal                              | pSport 1      | LP014                         |
| HFDM                       | Rectum tumour                              | pSport 1      | LP014                         |
| HGAM                       | Colon, normal                              | pSport 1      | LP014                         |
| HMM                        | Colon, tumour                              | pSport 1      | LP014                         |
| HCLB HCLC                  | Human Lung Cancer                          | Lambda Zap II | LP015                         |
| HRLA                       | L1 Cell line                               | ZAP Express   | LP015                         |
| HAM                        | Hypothalamus, Alzheimer's                  | pCMVSport 3.0 | LP015                         |
| HKBA                       | Ku 812F Basophils Line                     | pSport 1      | LP015                         |
| HS2S                       | Saos2, Dexamethosome Treated               | pSport 1      | LP016                         |
| HA5A                       | Lung Carcinoma A549 TNFalpha<br>activated  | pSport 1      | LP016                         |
| HTFM                       | TF-1 Cell Line GM-CSF Treated              | pSport 1      | LP016                         |
| HYAS                       | Thyroid Tumour                             | pSport 1      | LP016                         |
| HUTS                       | Larynx Normal                              | pSport 1      | LP016                         |
| HXOA                       | Larynx Tumor                               | pSport 1      | LP016                         |
| HEAH                       | Ea.hy.926 cell line                        | pSport 1      | LP016                         |
| HINA                       | Adenocarcinoma Human                       | pSport 1      | LP016                         |
| HRMA                       | Lung Mesothelium                           | pSport 1      | LP016                         |
| HLCL                       | Human Pre-Differentiated<br>Adipocytes     | Uni-Zap XR    | LP017                         |
| IS2A                       | Saos2 Cells                                | pSport 1      | LP020                         |
| IS2I                       | Saos2 Cells; Vitamin D3 Treated            | pSport 1      | LP020                         |
| HUCM                       | CHME Cell Line, untreated                  | pSport 1      | LP020                         |

| Libraries owned by Catalog             | Catalog Description                                                                   | Vector            | ATCC™<br>Deposit |
|----------------------------------------|---------------------------------------------------------------------------------------|-------------------|------------------|
| HEPN                                   | Aryepiglottis Normal                                                                  | pSport 1          | LP020            |
| HPSN                                   | Sinus Piniformis Tumour                                                               | pSport 1          | LP020            |
| INSA                                   | Stomach Normal                                                                        | pSport 1          | LP020            |
| INSM                                   | Stomach Tumour                                                                        | pSport 1          | LP020            |
| HNLA                                   | Liver Normal Met5No                                                                   | pSport 1          | LP020            |
| HUTA                                   | Liver Tumour Met 5 Tu                                                                 | pSport 1          | LP020            |
| HOCN                                   | Colon Normal                                                                          | pSport 1          | LP020            |
| HOCT                                   | Colon Tumor                                                                           | pSport 1          | LP020            |
| HTNT                                   | Tongue Tumour                                                                         | pSport 1          | LP020            |
| HLXN                                   | Larvnx Normal                                                                         | pSport 1          | LP020            |
|                                        |                                                                                       |                   |                  |
| ILXT                                   | Larynx Tumour                                                                         | pSport 1          | LP020            |
| HTYN                                   | Thymus                                                                                | pSport 1          | LP020            |
| IPLN                                   | Placenta                                                                              | pSport 1          | LP020            |
| HTNG                                   | Tongue Normal                                                                         | pSport 1          | LP020            |
| IZAA                                   | Thyroid Normal (SDCA2 No)                                                             | pSport 1          | LP020            |
| IWES                                   | Thyroid Thyroiditis                                                                   | pSport 1          | LP020            |
| IFHD                                   | Ficolled Human Stromal Cells, 5Fu treated                                             | pTrip1Ex2         | LP021            |
| HFHM,HFHN                              | Ficolled Human Stromal Cells,<br>Untreated                                            | pTrip1Ex2         | LP021            |
| HPCI                                   | Hep G2 Cells, lambda library                                                          | lambda Zap-CMV XR | LP021            |
| IBCA,HBCB,HBCC                         | H. Lymph node breast Cancer                                                           | Uni-ZAP XR        | LP021            |
| HCOK.                                  | Chondrocytes                                                                          | pSPORT1           | LP022            |
| IDCA, HDCB, HDCC                       | Dendritic Cells From CD34 Cells                                                       | pSPORT1           | LP022            |
| HDMA, HDMB                             | CD40 activated monocyte dendritic<br>cells                                            | pSPORT1           | LP022            |
| HDDM, HDDN, HDDO                       | LPS activated derived dendritic                                                       | pSPORT1           | LP022            |
| HPCR                                   | Hep G2 Cells, PCR library                                                             | lambda Zap-CMV XR | LP022            |
| НААА, НААВ, НААС                       | Lung, Cancer (4005313A3):<br>Invasive Poorly Differentiated Lung<br>Adenocarcinoma    | pSPORT1           | LP022            |
| HIPA, HIPB, HIPC                       | Lung, Cancer (4005163 B7):<br>Invasive, Poorly Diff.<br>Adenocarcinoma, Metastatic    | pSPORT1           | LP022            |
| НООН, НООІ                             | Ovary, Cancer: (4004562 B6)<br>Papillary Serous Cystic Neoplasm,<br>Low Malignant Pot | pSPORT1           | LP022            |
| HIDA                                   | Lung, Normal: (4005313 B1)                                                            | pSPORT1           | LP022            |
| HUJA,HUJB,HUJC,HUJD,HUJE               | B-Cells                                                                               | pCMVSport 3.0     | LP022            |
| INOA,HNOB,HNOC,HNOD                    | Ovary, Normal: (9805C040R)                                                            | pSPORT1           | LP022            |
| INLM                                   | Lung, Normal: (4005313 B1)                                                            | pSPORT1           | LP022            |
| ISCL                                   | Stromal Cells                                                                         | pSPORT1           | LP022            |
| HAAX                                   | Lung, Cancer: (4005313 A3)<br>Invasive Poorly-differentiated                          | pSPORT1           | LP022            |
|                                        | Metastatic lung adenocarcinoma                                                        |                   |                  |
| HUUA,HUUB,HUUC,HUUD                    | B-cells (unstimulated)                                                                | pTrip1Ex2         | LP022            |
| HWWA,HWWB,HWWC,HWWD,<br>HWWE,HWWF,HWWG | B-cells (stimulated)                                                                  | pSPORT1           | LP022            |
| HCCC                                   | Colon, Cancer: (9808C064R)                                                            | pCMVSport 3.0     | LP023            |
| HPDO HPDP HPDQ HPDR HPD                | Ovary, Cancer (9809C332): Poorly<br>differentiated adenocarcinoma                     | pSport 1          | LP023            |
| НРСО НРСР НРСО НРСТ                    | Ovary, Cancer (15395A1F): Grade<br>II Papillary Carcinoma                             | pSport 1          | LP023            |

| Libraries owned by Catalog  | Catalog Description                                                                    | Vector   | ATCC <sup>TM</sup><br>Deposit |
|-----------------------------|----------------------------------------------------------------------------------------|----------|-------------------------------|
| НОСМ НОСО НОСР НОСО         | Ovary, Cancer: (15799A1F) Poorly<br>differentiated carcinoma                           | pSport 1 | LP023                         |
| HCBM HCBN HCBO              | Breast, Cancer: (4004943 A5)                                                           | pSport 1 | LP023                         |
| HNBT HNBU HNBV              | Breast, Normal: (4005522B2)                                                            | pSport 1 | LP023                         |
| HBCP HBCQ                   | Breast, Cancer: (4005522 A2)                                                           | pSport 1 | LP023                         |
| HBCJ                        | Breast, Cancer: (9806C012R)                                                            | pSport 1 | LP023                         |
| HSAM HSAN                   | Stromal cells 3.88                                                                     | pSport 1 | LP023                         |
| HVCA HVCB HVCC HVCD         | Ovary, Cancer: (4004332 A2)                                                            | pSport 1 | LP023                         |
| HSCK HSEN HSEO              | Stromal cells (HBM3.18)                                                                | pSport 1 | LP023                         |
| HSCP HSCQ                   | stromal cell clone 2.5                                                                 | pSport 1 | LP023                         |
| HUXA                        | Breast Cancer: (4005385 A2)                                                            | pSport 1 | LP023                         |
| HCOM HCON HCOO HCOP<br>HCOQ | Ovary, Cancer (4004650 A3): Well-<br>Differentiated Micropapillary<br>Serous Carcinoma | pSport 1 | LP023                         |
| HBNM                        | Breast, Cancer: (9802C020E)                                                            | pSport 1 | LP023                         |
| HVVA HVVB HVVC HVVD<br>HVVE | Human Bone Marrow, treated                                                             | pSport 1 | LP023                         |

[0697] Two nonlimiting examples are provided below for isolating a particular clone from the deposited sample of plasmid cDNAs cited for that clone in Table 7. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO.X.

possible polymucleotide with 30-40 mucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with \$^3P\_7-ATP using T4 polymucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982)). The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

[0699] Alternatively, two primers of 17-20 nucleotides derived from both ends of the nucleotide sequence of SEQ ID NO.X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA

band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[0700] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 5' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993)).

[0701] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

10702] This above method starts with total RNA isolated from the desired source, although poly-A+RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

1003] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired S' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the S' end sequence belongs to the desired gene.

## Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

107041 A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO.X according to the method described in Example 1. (See also, Sumbrook.)

# Example 3: Tissue specific expression analysis

10705] The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue and/or disease specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs and assembled contigs which show tissue specific expression are selected.

[9706] The original clone from which the specific EST sequence was generated, or in the case of an assembled contig, the clone from which the 5° most EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured and then transferred in 96 or 384 well format to a nylon membrane (Schleicher and Scheill) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known

tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

[10707] Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed (e.g., prostate, prostate, cancer, ovarian, ovarian cancer, etc.). The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuii phosphorimager.

[0708] Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified.

#### Example 4: Chromosomal Mapping of the Polynucleotides

107091 An oligonucleotide primer set is designed according to the sequence at the 5° end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions: 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions are analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

## Example 5: Bacterial Expression of a Polypeptide

[0710] A polymucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5° and 3° ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHl and Xbal, at the 5° end of the primers in order to clone the amplified product into the expression vector. For example, BamHl and Xbal correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (AmpP), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

107111 The pQE-9 vector is digested with BamHI and Xhal and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacl repressor and also confers kanamycin resistance (Kan<sup>4</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[0712] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O/D 200) of between

0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM.
IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

10713] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guandine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supermatant containing the polypeptide is loaded onto a nickel-nitrile-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., supra). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The OIAexpressionist (1995) OIAGEN, Inc., supra).

10714] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is cluted with 6 M guanidine-HCl, pH 5.

10715] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl. 20% glycerol, 20 mM Tris/HCl pH 7-4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at 80°C.

10716] In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC™ Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC™ Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycimphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (laclq). The origin of replication (oric') is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

107171 DNA can be inserted into the pHE4a by restricting the vector with Ndel and Xbal, BamHI, Xbol, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for Ndel (s' primer) and Xbal, BamHI, Xbol, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are lizated according to standard protocols.

[0718] The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

## Example 6: Purification of a Polypeptide from an Inclusion Body

[0719] The following alternative method can be used to purify a polypeptide expressed in E coli when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

[0720] Upon completion of the production phase of the E. coli fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

107211 The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pft 7.4.

10722] The resulting washed inclusion bodies are solubilized with 1.5 M guantidine hydrochloride (GuHCI) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supermatent is incubated at 4°C overnight to allow further GuHCI extraction.

[9723] Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

10724] To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and clutted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 mm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

[0725] Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A<sub>280</sub> monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

19726] The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ne/ml according to LAL assays.

#### Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

[0727] In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from E. coli under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polybedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polymucleotide.

[0728] Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

10729] Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

[0730] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

10731] The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GENECLEAN®" BIO 101 Inc., La Jolla, Ca.).

[0732] The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. E. coll HB101 or other suitable E. coll hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

[0733] Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BACULOGOLD"<sup>36</sup> baculovirus DNA, Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BACULOGOLD<sup>36</sup> virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC<sup>764</sup> CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal eaff serum is added. Cultivation is then continued at 27° C for four days.

10734] After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, supra. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect S/9 cells seeded in 35 mm disbes. Four days later the supernatants of these culture disbes are harvested and then they are stored at 4° C.

10735] To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated F183. The cells are infected with the recombinant baculovirus containing the polymeleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of <sup>28</sup>S-methionine and 5 μCi <sup>28</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supermatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

[0736] Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

# Example 8: Expression of a Polypeptide in Mammalian Cells

[0737] The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[9738] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC™ 57152), pSV2dhfr (ATCC™ 37146), pBC12M1 (ATCC™ 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, 119 and Jurkat cells, mouse NH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[0739] Alternatively, the polypeptide can be expressed in stable cell lines containing the polymucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hydromycin allows the identification and isolation of the transfected cells.

[0740] The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357Sydenham, M. A., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., BioTechnology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins. [9741] Derivatives of the plasmid pSV2-dflif (ATCC<sup>TM</sup> Accession No. 27146), the expression vectors pC4 (ATCC<sup>TM</sup> Accession No. 209646) and pC6 (ATCC<sup>TM</sup> Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhanner (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, Xbal and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preprotinsulin sene, and the mouse DHFR gene under control of the SV40 early promoter.

1370 (1978); Hamlin, J. L. and Ma, C., Biochem, et Biophys, Acta, 1097:107-143 (1990); Page, M. J. and

[0742] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% against eet.

[0743] A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[0744] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[0745] The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid o C6 using. for instance, restriction enzyme analysis.

10746] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pCG or pC4 is cotransfected with 0.5 μg of the plasmid pSVreo using lipofectin (Felgner et al., supra). The plasmid pSV2-neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μΜ, 2 μΜ, 5 μΜ, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of

100 - 200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

## Example 9: Protein Fusions

[0747] The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to Histag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5, see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988)). Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflift time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent beterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

[0748] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

10749] For example, if pC4 (ATCC<sup>TM</sup> Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced. [0750] If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 9674891.)

## Human IgG Fc region:

# GAACGTCTTCCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC TCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEO ID NO: 1)

## Example 10: Production of an Antibody from a Polypeptide

## a) Hybridoma Technology

[0751] The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of a polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisers of greater specific activity.

Monoclonal antibodies specific for a polypeptide of the present invention are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with a polypeptide of the present invention or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

[0753] The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCCTM. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to a polypeptide of the present invention can be produced in a two-step procedure using anti-diotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide-specific antibody can be blocked by said polypeptide. Such antibodies comprise antiidiotypic antibodies to the polypeptide-specific antibody and are used to immunize an animal to induce formation of further polypeptide-specific antibodies.

[0755] For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are

discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816.567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., International Publication No. WO 8702671; Boultianne et al., Nature 312-643 (1984); Neuberger et al., Nature 314:268 (1985)).

b) Isolation Of Antibody Fragments Directed Against a Polypeptide of the Present Invention From A Library Of seFvs

[0756] Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against a polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

10757] Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody fragments, approximately 10° E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in International Publication No. WO 92/01047.

10758] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avditty of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37°C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 m1 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10<sup>30</sup> transducing units/ml (ampicillin-resistant clones).

[0799] Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10<sup>13</sup> TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are clutted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-ICL, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating cluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage

for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

(1976) Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble seFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., International Publication No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

[0761] RNA isolated from entire families or individual patients presenting with diabetes mellitus is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO.X; and/or the nucleotide sequence of the cDNA contained in ATCCT<sup>TM</sup> Deposit No.Z. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polymucleotide kinase, employing SEQUITHERM™ Polymerase (Epicentre Technologies). The intron-exon boundaries of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing.

[0763] PCR products are cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

[0764] Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-I DNA for specific hybridization to the corresponding genomic locus.

(19765] Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometries, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991)). Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diaenostic marker for an associated disease.

#### Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

[0766] A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

[0767] For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

10788] The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound no/bvertide.

[0769] Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

[0770] Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

#### Example 13: Formulation

107711 The invention also provides methods of preventing, treating and/or ameliorating diabetes mellitus by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

[0772] The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[0773] As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1.4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of

treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[0774] Therapeutics can be are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular infection and infusion.

[0775] Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intrastricular injection and infusion.

[0776] Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

[10777] Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D-(+)3-hydroxybutyric acid (EP 133,988).

[0778] In a preferred embodiment, polypeptide, polynucleotide, and antibody compositions of the invention are formulated in a biodegradable, polymeric drug delivery system, for example as described in U.S. Patent Nos. 4,938,763; 5,278,201; 5,278,202; 5,324,519; 5,340,849; and 5,487,897 and in International Publication Numbers WOOI/35929, WOO0/24374, and WOOI/06117 which are hereby incorporated by reference in their entirety. In specific preferred embodiments the polypeptide, polynucleotide, and antibody compositions of the invention are formulated using the ATRIGEL® Biodegradable System of Atrix Laboratories. Inc. (Fort Collins, Colorado).

[0779] Examples of biodegradable polymers which can be used in the formulation of polypeptide, polymucleotide, and antibody compositions, include but are not limited to, polylactides, polygylcolides, polycaprolactones, polyantydrides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthoearbonates, polyphosphazenes, polyhydroxyburyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(mino acids), poly(methyl vinyl ether), poly(malic anhydride), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those that have a lower degree of

crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more amorphous regions to enhance solubility. In specific preferred embodiments, the biodegradable polymers which can be used in the formulation of polypeptide, polymecleotide, and antibody compositions are poly(lactide-coglycolides). Polymer properties such as molecular weight, hydrophobicity, and lactide/glycolide ratio may be modified to obtain the desired polypeptide, polynucleotide, or antibody release profile (See, e.g., Ravivarapu et al., Journal of Pharmaceutical Sciences 89:732-741 (2000), which is hereby incorporated by reference in its entirety).

107801 It is also preferred that the solvent for the biodegradable polymer be non-toxic, water miscible, and otherwise biocompatible. Examples of such solvents include, but are not limited to, N-methyl-2pyrrolidone, 2-pyrrolidone, C2 to C6 alkanols, C1 to C15 alchohols, dils, triols, and tetraols such as ethanol, glycerine propylene glycol, butanol; C3 to C15 alkyl ketones such as acetone, diethyl ketone and methyl ethyl ketone; C3 to C15 esters such as methyl acetate, ethyl acetate, ethyl lactate; alkyl ketones such as methyl ethyl ketone, C1 to C15 amides such as dimethylformamide, dimethylacetamide and caprolactam; C3 to C20 ethers such as tetrahydrofuran, or solketal; tweens, triacetin, propylene carbonate. decylmethylsulfoxide, dimethyl sulfoxide, oleic acid, 1-dodecylazacycloheptan-2-one. Other preferred solvents are benzyl alchohol, benzyl benzoate, dipropylene glycol, tributyrin, ethyl oleate, glycerin, glycofural, isopropyl myristate, isopropyl palmitate, oleic acid, polyethylene glycol, propylene carbonate, and triethyl citrate. The most preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, triacetin, and propylene carbonate because of the solvating ability and their compatibility. [0781] Additionally, formulations comprising polypeptide, polynucleotide, and antibody compositions and a biodegradable polymer may also include release-rate modification agents and/or pore-forming agents. Examples of release-rate modification agents include, but are not limited to, fatty acids, triglycerides, other like hydrophobic compounds, organic solvents, plasticizing compounds and hydrophilic compounds. Suitable release rate modification agents include, for example, esters of mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as propylene glycol, polyethylene glycol, glycerin, sorbitol, and the like; fatty acids; triesters of glycerol, such as triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols, such as cholesterol; alcohols, such as C.sub.6 -C.sub.12 alkanols, 2-ethoxyethanol. The release rate modification agent may be used singly or in combination with other such agents. Suitable combinations of release rate modification agents include, but are not limited to, glycerin/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, butylene glycol/adipic acid, and the like. Preferred release rate modification agents include, but are not limited to, dimethyl citrate, triethyl citrate, ethyl heptanoate, glycerin, and hexanediol, Suitable pore-forming agents that may be used in the polymer composition include, but are not limited to. sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, polymers such as

hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. Solid crystals that will provide a defined pore size, such as salt or sugar, are preferred.

[0782] In specific preferred embodiments the polypeptide, polypucleotide, and antibody compositions of the invention are formulated using the BEMA™ BioTordible Mucoadhesive System, MCA™ MucoCutaneous Absorption System, SMP™ Solvent MicroParticle System, or BCP™ BioCompatible Polymer System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

0783] Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (see generally, Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317-327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per see DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. (USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-1,18008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unlamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic. [0784] In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a

[0784] In yet an additional embodiment, the Therapeuties of the invention are delivered by way of a pump (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

[0785] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

10786] For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

[0787] Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as linosomes.

19788] The currier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other earbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols

such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[0789] The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[0790] Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a storper pierceable by a hypodermic injection needle.

[0791] Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

[0792] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Theraneutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to. alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), OS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable prepartions of Corvnebacterium parvum. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdiuVax 100a, OS-21, OS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholcra, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0794] The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of

the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADONTM), acenocoumarol (e.g., nicoumalone, SINTHROMETM), indan-1,3-dione, phenprocoumon (e.g., MARCUMARTM), ethyl biscoumacetate (e.g., TROMEXANIM), and aspirin. In a specific embodiment, compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment. compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are administered in combination with heparin and aspirin. In another embodiment, the Therapeutics of the invention are administered in combination with [0796] thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASETM), antiresplace (e.g., EMINASETM), tissue plasminogen activator (t-PA, altevase, ACTIVASETM), urokinase (e.g., ABBOKINASETM), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICARTM). In a specific embodiment, compositions of the invention are administered in combination with tissue plasminogen activator and aspirin.

[0797] In another embodiment, the Therapeutics of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINETM), and ticlopidine (e.g., TICLIDTM).

[0798] In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombobytic drugs and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet,

anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0799] In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T). EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delayirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection. [0800] Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity in vitro; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281). Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the 108011 HEPT class: Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delayirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation: DuPont): GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants: Glaxo Wellcome): CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830). 108021 Additional protease inhibitors include LOPINAVIR™ (ABT378/r: Abbott Laboratories): BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with in vitro activity against protease

inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE<sup>TM</sup> (amprenavir; Glaxo Wellcome Inc.).

[0803] Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor: Trimeris).

[0804] Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists.

Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine receptor agonists such as RANTES, SDF-1, MIP-10. MIP-10. tec., may also inhibit fusion.

[1805] Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylqutinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZDNTEVIR™ (AR 177, an oligonucleotide that probably acid at cell surface rather than being a true integrase inhibitor; Arondex), and naphthols such as those disclosed in WO 98:50347. [18066] Additional antiretroviral agents include hydroxyurea-like compunds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

[0807] Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

[0808] Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-α/2a; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang et al., PNAS 94:11567-72 (1997); Chen et al., Nat. Med. 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 1205; the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17, 84d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies anti-TXFα antibodies, and monoclonal antibody 33A, aryl hydrocarbon (AH) receptor agonists

and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and  $\alpha$ naphthoflavone (WO 98/30213); and antioxidants such as  $\gamma$ -L-glutamyl-L-cysteine ethyl ester ( $\gamma$ -GCE; WO 99/56764).

[0809] In a further embodiment, the Therapeuties of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeuties of the invention include, but are not limited to, acvelovir, ribavirin, amantadine, and remantidine.

108101 In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, trimethoprim-sulfamethoxazole, dapsone, pentamidine, atoyaquone, isoniazid, rifampin, pyrazinamide, ethambutol, rifabutin, clarithromycin, azithromycin, ganciclovir, foscarnet, cidofovir, fluconazole, itraconazole, ketoconazole, acyclovir, famciclovir, pyrimethamine, leucovorin, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with trimethoprim-sulfamethoxozole, dapsone, pentamidine, and/or atovaçuone to prophylactically treat or prevent an opportunistic Pneumocystis carinii pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with isoniazid, rifampin, pyrazinamide, and/or ethambutol to prophylactically treat or prevent an opportunistic Mycobacterium avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with rifabutin, clarithromycin, and/or azithromycin to prophylactically treat or prevent an opportunistic Mycobacterium tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ganciclovir, foscarnet, and/or cidofovir to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with fluconazole, itraconazole, and/or ketoconazole to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with acyclovir and/or famciclovir to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with pyrimethamine and/or leucovorin to prophylactically treat or prevent an opportunistic Toxoplasma gondii infection. In another specific embodiment, Therapeutics of the invention are used in any combination with leucovorin and/or NEUPOGEN™ (filgrastim/G-CSF) to prophylactically treat or prevent an opportunistic bacterial infection.

[0811] In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

[0812] In other embodiments, the Therapeutics of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the Therapeutics of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

[0813] In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrevate, thalidomide, methossalen, rapamycin, leftmomide, mizuribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™ (cyclosporine), NEORAL™ (cyclosporine), Geyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirclimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0814] In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR<sup>101</sup>, IVEEGAM<sup>111</sup>, SANDOGLOBULIN<sup>102</sup>, GAMMAGARD S/D<sup>102</sup> (immune globulin), ATGAM<sup>103</sup> (antithymocyte globulin), and GAMIMUNIE<sup>103</sup> (immune globulin). In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0815] In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisolone, prodnisolone, nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylacethoxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfizzone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, piloxime, proquazone, proxazole, and tenidap.

[0816] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, pachitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0817] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0818] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate by the suitable vanadyl sulfate including vanadyl sulfate by the sulfate including vanadyl sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by the sulfate by

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable molybden oxides include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates, Suitable molybdenum oxide, include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdenum oxides include molybdenum (VI) oxide, and molybdenum oxides include molybdenum (VI) oxide, and molybdenum oxides include molybdenum (VI) oxide, and molybdenum oxides include molybdenum oxide, sodium molybdenum (VI) oxide, and molybdenum oxide, and molybdenum oxides include molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, sodium molybdenum oxide, so

A wide variety of other anti-angiogenic factors may also be utilized within the context of the [0820] present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d.L-3,4dehydroproline, Thiaproline, alpha, alpha, dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Payloff et al., J. Bio, Chem. 267:17321-17326, (1992)): Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348;555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin, Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

[0821] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman J Pediatr. Surg. 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., J Clin. Invest. 103:47-54 (1999)); carboxynaminolmidazole; Carboxynamidotriazole (CAD) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101
AstraZencea (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octrootide (Somatostatin); Pamertin; Penacillamine; Photopoint; Pl-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorotracil.

108221 Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not lmited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Fov, Ouebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not lmited to, EMD-121974 (Merck KegaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

10823] In particular embodiments, the use of compositions of the invention in combination with aniangiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

108241 In a particular embodiment, the use of compositions of the invention in combination with antiangiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[0825] In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[0826] In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercantopurine (6-mercantopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

[0827] In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximal (also known as REMICADE™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as ARAVA™ from Hoechst Marion Roussel), KINERET™ (an IL-1 Receptor aniagonist also known as Anakirar from Amgen, Inc.)

[0828] In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or

anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly evelophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs. [0829] In another specific embodiment, the compositions of the invention are administered in combination with ZEVALIN™ (indictor). In a further embodiment, compositions of the invention are administered with ZEVALIN™ (indiclor) and CHOP, or ZEVALIN™ (indiclor) and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. ZEVALIN™ (indictor) may be associated with one or more radisotopes. Particularly preferred isotopes are 90Y and 111In. [0830] In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-lalpha, IL-lbeta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21. In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas. CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153. 108321 In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to. Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317: Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993): Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO

90/1349; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number IP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-8186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

[0833] In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

10834 In an additional embodiment, the Therapeuties of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeuties of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (GCSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

(8835) In certain embodiments, Therapeuties of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, exprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

[0836] In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxim, digitoxim, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quimdine, sotalol, tocainide, and verapamil).

[0837] In another embodiment, the Therapetuics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na<sup>+</sup>K<sup>+</sup>2CT symport (e.g., firosemide, burnetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorothiadidone, indapamide, metolazone, and quincthazone), potassium sparing diuretics (e.g., amiloride and trianterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

[0838] In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, <sup>127</sup>I, radioactive isotopes of iodine such as <sup>131</sup>I and <sup>123</sup>I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatronin); growth hormone.

analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octrootide); gonadotropin preparations such as PREGNYL™, A.P.L™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSI)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (gossrelin acetate), SUPPRELIN™ (instrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (gossrelin acetate), Suprhetic preparations of thyrotropin-releasing hormone such as RELEFACT TRI™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™, synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T₄™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T₃™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-n-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca²¹ channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (fopanoic acid) and ORAGRAFIN™ (sodium ipodate).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinvl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone). ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol). PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinvl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel). DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-OD™ (norethindrone), and OVRETTE™ (norgestrel).

[0840] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acctate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone canathate), DEPO-TESTOSTERONE™ (testosterone evojonate). DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone): testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate). DIPROSONE™ (betamethasone dipropionate). CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate). CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone). CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone); bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), ciglitazone. pioglitazone, and alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide): and diazoxides such as PROGLYCEM™ (diazoxide).

[0841] In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOLTM), ferrous fumarate (e.g., FEOSTATTM), ferrous gluconate (e.g., FERGONTM), polysaccharide-iron complex (e.g., NIFEREXTM), iron dextran injection (e.g., INFEDTM), cupric sulfate, pyroxidine, riboflavin, Vitamin B<sub>12</sub>, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PCTM), hydroxocobalamin, folic acid (e.g., FOLVITETM), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin. In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

108431 In certain embodiments, the Therapeutics of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the Therapeutic of the invention include, but are not limited to, H2 histamine receptor antagonists (e.g., TAGAMET<sup>™</sup> (cimetidine), ZANTAC<sup>™</sup> (ranitidine), PEPCID<sup>™</sup> (famotidine), and AXID<sup>™</sup> (nizatidine)); inhibitors of H<sup>+</sup>, K<sup>+</sup> ATPase (e.g., PREVACID<sup>TM</sup> (lansoprazole) and PRILOSEC<sup>TM</sup> (omegrazole)); Bismuth compounds (e.g., PEPTO-BISMOLTM (bismuth subsalicylate) and DE-NOLTM (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTECTM (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTILTM (diphenoxylate), MOTOFENTM (diphenoxin), and IMODIUMTM (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN<sup>TM</sup> (octreotide), antiemetic agents (e.g., ZOFRANTM (ondansetron), KYTRILTM (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

[0844] In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

[10845] The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of polypeptides (including agonists thereto), and/or antibodies of the invention. Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual may be treated by

administering agonists of said polypeptide. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist (including polypeptides and antibodies of the present invention) to increase the activity level of the polypeptide in such an individual.

[0846] For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation are provided in Example 13.

# Example 15: Method of Treating Increased Levels of the Polypeptide

10847] The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

[0848] In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

[0849] For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 2.1 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The antisense polynucleotides of the present invention can be formulated using techniques and formulations described herein (e.g. see Example 13), or otherwise known in the art.

#### Example 16: Method of Treatment Using Gene Therapy-Ex Vivo

[0880] One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

(0851) At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into lareer flasks.

[0852] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads. [0853] The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the

presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

108541 The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

108551 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced. The engineered fibroblasts are then transplanted onto the host, either alone or after having been

grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention Another method of gene therapy according to the present invention involves operably

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associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO; 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA, 86:8932-8935 (1989); and Zijlstra et al., Nature, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired. [0858] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of

the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. 108591 The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel, then purified by phenol extraction and ethanol precipitation.

[0860] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfectionfacilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[0861] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Pibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supermatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub> HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the supermatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3X10<sup>6</sup> cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a 108631 plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid. [0864] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately 1.5.X106 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 uF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[8665] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[0866] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

Mother aspect of the present invention is using in vivo gene therapy methods to prevent, treat, and/or ameliorate diabetes mellitus. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polymeleotide of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, Wo90/11092, WO98/11779, U.S. Patent NO. 5693622, 5705151, 5580859, Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

[9888] The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or anueous carrier.

[9869] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0871] The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacumae of bone. It is similarly the space occupied by the plasma of the circulation and be lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising

these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

10872] For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.005 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0873] The dose response effects of injected polynucleotide in muscle in vivo is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Pive to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[0875] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

#### Example 19: Transgenic Animals

10876] The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

(1987) Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo., 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 299:1745 (1993); introducing nucleic scid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lawitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

[0878] Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 380:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, i.e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

[0880] Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of

transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

10881] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonics of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

10882] Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### Example 20: Knock-Out Animals

108831 Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (e.g., see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention in vivo. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site in vivo using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient in vivo. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell

genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intrapritioneally.

[0885] Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligam & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

[0886] When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

[0887] Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 21: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models
Diabetic db+/db+ Mouse Model.

108881

[0889] To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. et al., J. Surg. Res. 52:389 (1992); Greenhalgh, D.G. et al., Am. J. Pathol. 136:1235 (1990).

[0890] The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (dh+/dh+) mice are obese in comparison to their normal heterozygous (db+/dh+) littermates. Mutant diabetic (db+/dh+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman et al. Proc. Natl. Acad. Sci. USA 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/dh+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel et al., J. Immunol. 120:1375 (1978); Debray-Sachs, M. et al., Clin. Exp. Immunol. 51(1):1-7 (1983); Leiter et al., Am. J. of Pathol. 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. et al., Exp. Neurol. 83/2):221-232 (1984); Robertson et al., Diabetes 29(1):60-67 (1980); Giacomelli et al., Lab Invest. 40(4):460-473 (1979); Coleman, D.L., Diabetes 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel et al., J. Immunol. 120:1375-1377 (1978)).

[0891] The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, et al., Am. J. of Pathol. 136:1235-1246 (1990)).

[0892] Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[9893] Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., J. Exp. Med. 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitioneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are entity cleansed with sterile saline and sauze sponses.

108841 Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

10885] An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.
10896 | Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[0897] Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

10888] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal runch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

[0899] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-cosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by

treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. et al., Am. J. Pathol. 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

[10000] Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of recpithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

[0902] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

Steroid Impaired Rat Model

[0903] The inhibition of wound healing by steroids has been well documented in various in vitro and in vivo systems (Wahl, Glucocorticoids and Wound healing. In: Amti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet al., J. Immunol. 115: 476-481 (1975); Werb et al., J. Exp. Med. 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert et al., An. Intern. Med. 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck et al., Growth Factors. 5: 295-304 (1991); Haynes et al., J. Clin. Invest. 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., J. Clin. Invest. 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck et al., Growth Factors. 5: 295-304 (1991); Haynes et al., J. Clin. Invest. 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989), Pierce et al., Proc. Natl. Acad. Sci. USA 86: 2229-2233 (1989)).

[9094] To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

[9095] Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

10906] The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% channol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponses.

[0907] Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[9008] The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution. [9009] Animals are enthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in

[0910] Three groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[0911] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

[19912] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-cosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

[0913] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

10914 The studies described in this example tested activity of agonists or antagonists of the invention.
However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polynentides of the invention (e.g., sene therapy).

Example 22: Production Of Polypeptide of the Invention For High-Throughput Screening
Assays

[9015] The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 24-27. [9016] First, dilute Poly-D-Lysine (644 587 Bochringer-Mannheim) stock solution (I mg/ml in PBS) 1:20 in PBS (two calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

[0917] Plate 293T cells (do not carry cells past P+20) at 2 x 10° cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium/with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker)/10% heat inactivated FBS(14-503F Biowhittaker)/12 Penstrep(17-602E Biowhittaker). Let the cells grow overnight. [1918] The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimen I (31985070 Gibco/BRL)96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimen I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

10919] Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

190201 While cells are incubating, prepare appropriate media, either 19/aBSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L CuSO<sub>4</sub>-5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>-9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>-7H<sub>2</sub>O; 311.80 mg/L of Kcl; 28.64 mg/L of MgCl<sub>2</sub>: 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>-H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HFO<sub>4</sub>: 4320 mg/L of ZnSO<sub>4</sub>-7H<sub>2</sub>O; 0.02 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; 0.070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Dl-alpha-Tocopherol-Acetate; 0.0520 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L-Alanine; 147.50 mg/ml of L-Agrarine-HCL; 7.50 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL+1<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of Glycine;

52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>0; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Propine; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Tripronine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryptosine-2Na-2H<sub>2</sub>0; and 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of Inoisotic; 3.02 mg/L of Pyridoxine HCL; 0.319 mg/L of Ribotlavin; 3.17 mg/L of Myridoxine HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Ribotlavin; 3.17 mg/L of Thismine HCL; 0.365 mg/L of Thipmidine; 0.680 mg/L of Yitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrue; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 m/Osm) with 2mm glutamine and 1x penstrep. (BSA (81-06x-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

[0921] The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

[0922] On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 24-27.

[1022] It is specifically understood that when activity is obtained in any of the assays described below using a supermatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supermatant. Thus, the invention further provides a method of identifying the protein in the supermatant characterized by an activity in a particular assay.

# Example 23: Construction of GAS Reporter Construct

[0024] One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements after the expression of the associated gene.

[0925] GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in Thelper class 1, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

[0926] The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

[0927] The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995)). A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class I includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Tm-Ser-Xaa-Tm-Ser (SEO ID NO: 2)).

[0928] Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway (See Table below). Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

| Ligand                                                                                                                                                                     | tyk2                         | JAKs<br>Jak1          | Jak2                       | Jak3                               | STATS GAS(elements) or ISRE                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------|----------------------------|------------------------------------|--------------------------------------------------------------------------------|
| IFN family<br>IFN-a/B +<br>IFN-g<br>II-10                                                                                                                                  | +                            | -<br>+<br>?           | -<br>+<br>?                | 1,2,3                              | ISRE<br>1 GAS (IRF1>Lys6>IFP)                                                  |
| gp130 family<br>IL-6 (Pleiotropic) +<br>Il-11 (Pleiotropic) ?<br>OnM(Pleiotropic)?<br>LIF(Pleiotropic) ?<br>CNTF(Pleiotropic)<br>G-CSF(Pleiotropic)<br>IL-12 (Pleiotropic) | +<br>+<br>+<br>+<br>-/+<br>? | +<br>?<br>+<br>+<br>+ | ?<br>?<br>?<br>?<br>+<br>? | 1,3<br>1,3<br>1,3<br>1,3<br>2<br>? | GAS (IRF1>Lys6>IFP)  1,3 1,3 1,3                                               |
| g-C family IL-2 (lymphocytes) IL-4 (lymph/myeloid) IL-7 (lymphocytes) IL-9 (lymphocytes) IL-13 (lymphocyte) IL-15                                                          |                              | + + + + + + +         | -<br>-<br>-<br>-<br>?<br>? | +<br>+<br>+<br>+<br>?<br>+         | 1,3,5 GAS<br>6 GAS (IRF1 = IFP >> Ly6)(IgH<br>5 GAS<br>5 GAS<br>6 GAS<br>5 GAS |
| gp140 family<br>IL-3 (myeloid)<br>IL-5 (myeloid)<br>GM-CSF (myeloid)<br>Growth hormone family<br>GH                                                                        | -<br>-<br>-<br>?             | -                     | + + + +                    | -                                  | 5 GAS (IRF1>IFP>>Ly6)<br>5 GAS<br>5 GAS                                        |
| PRL<br>EPO                                                                                                                                                                 | ?                            | -<br>+/-<br>-         | ++++                       | -                                  | 1,3,5<br>5 GAS(B-CAS>IRF1=IFP>>Ly                                              |
| Receptor Tyrosine Kinas<br>EGF<br>PDGF<br>CSF-1                                                                                                                            | es<br>?<br>?<br>?            | +<br>+<br>+           | +++++                      | :                                  | 1,3 GAS (IRF1)<br>1,3<br>1,3 GAS (not IRF1)                                    |

[1022] To construct a synthetic GAS containing promoter element a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994)), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an Xhol site. The sequence of the 5' primer is:

19030] 5':GGCCTTGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATTAGATT

5':GCGCAAGCTTTTGCAAAGCCTAGGC:3' (SEQ ID NO: 4)PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with Xhol/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCATAGATTTCCCCGAAATGATTTCCCCGAAA TATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTA ACTCCGCCCAGTTCCGCCCATTCTCCCGCCCATGGCTGACTAATTTTTTTATTATGCAGAGGC CGAGGCCGCCTCGGCCCTCTAGCTATTCCAGAAGTAGTGAGGAGGCCTTTTTTGGAGGGCCTAGGC TTTTGCAAAAAGCTT:' (SEO ID NO: 5)

[0931] With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

10932] The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and Xhol, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

100331 Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP easestie is removed from the GAS-SEAP vector using Sall and Notl, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding.

10934] Other constructs can be made using the above description and replacing GAS with a different promoter sequence, for example, with EGR and NF-KB promoter sequences. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct

activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

# [0935] Example 24: Assay for SEAP Activity

19036] SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

10937] Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

[1938] Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the Table below). Add 50 ml Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiltuminescent signal is ime dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

[0939] Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

| Reaction |  |  |
|----------|--|--|
|          |  |  |

| # of plates | Rxn buffer diluent (ml) | CSPD (ml) |
|-------------|-------------------------|-----------|
| 10          | 60                      | 3         |
| 11          | 65                      | 3.25      |
| 12          | 70                      | 3.5       |
| 13          | 75                      | 3.75      |
| 14          | 80                      | 4         |
| 15          | 85                      | 4.25      |
| 16          | 90                      | 4.5       |
| 17          | 95                      | 4.75      |
| 18          | 100                     | 5         |
| 19          | 105                     | 5.25      |
| 20          | 110                     | 5.5       |
| 21          | 115                     | 5.75      |
| 22          | 120                     | 6         |
| 23          | 125                     | 6.25      |
| 24          | 130                     | 6.5       |
| 25          | 135                     | 6.75      |
| 26          | 140                     | 7         |
| 27          | 145                     | 7.25      |
| 28          | 150                     | 7.5       |
| 29          | 155                     | 7.75      |
| 30          | 160                     | 8         |
| 31          | 165                     | 8.25      |
| 32          | 170                     | 8.5       |
| 33          | 175                     | 8.75      |
| 34          | 180                     | 9         |
| 35          | 185                     | 9.25      |
| 36          | 190                     | 9.5       |
| 37          | 195                     | 9.75      |
| 38          | 200                     | 10        |
|             |                         |           |

| 39 | 205 | 10.25 |
|----|-----|-------|
| 40 | 210 | 10.5  |
| 41 | 215 | 10.75 |
| 42 | 220 | 11    |
| 43 | 225 | 11.25 |
| 44 | 230 | 11.5  |
| 45 | 235 | 11.75 |
| 46 | 240 | 12    |
| 47 | 245 | 12.25 |
| 48 | 250 | 12.5  |
| 49 | 255 | 12.75 |
| 50 | 260 | 13    |

Example 25: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

[0940] Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

10941] The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.: catalog no. F-14202) used here.

[0942] For adherent cells, seed the cells at 10,000-20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

[0943] A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer

[9944] For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x.10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

[0945] For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

[19946] To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera Fistop is F/2; (4) Excitation is 488 m; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 mm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca<sup>++</sup> one centration.

### Example 26: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

[0947] The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and eytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

[1048] Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the sre-family (e.g., src, yes, lek, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leotin).

[0949] Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

[19550] Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (8t. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

[0951] To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 22, the medium was removed and 100 ml 10 extraction buffer (C20 mM

HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

[0952] Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

10953] Generally, the tyrosine kinase activity of a supermatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase ede2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

100401 The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg2+, (5mM ATP/5mM MgCl2), then 10ul of 5x Assay Buffer (40mM midazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl2, 5 mM MnCl2, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

[0955] The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

10956] Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase/anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

109571 Next add 100ul of peroxidase substrate solution (Bochringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 mm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 27: High-Throughput Screening Assay Identifying Phosphorylation Activity

[1958] As a potential alternative and/or complement to the assay of protein tyrosine kinase activity
described in Example 26, an assay which detects activation (phosphorylation) of major intracellular signal
transduction intermediates can also be used. For example, as described below one particular assay can detect
tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules,
such as Raf, JNK, 638 MAP, Man kinase kinase (MEK), MEK kinase, Src. Muscle specific kinase (MuSK).

IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

[0059] Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1 ml of protein G (lug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

[9960] A431 cells are seeded at 20,000/well in a 96-well Loprocybre filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supermatants obtained in Example 22 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

109611 After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is intriplated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

## Example 28: Detection of Inhibition of a Mixed Lymphocyte Reaction

19962] This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

[9063] Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus crythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

1964| Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM\*, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10<sup>6</sup> cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10<sup>6</sup> cells/ml. Fifly microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1.4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 µg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 µg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1 µC of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

[9065] Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, arti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supermatant), which enhances proliferation of lymphocytes.

(1986d) One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

## Example 29: Assays for Protease Activity

[1967] The following assay may be used to assess protease activity of the polypeptides of the invention.

[1968] Gelatin and casein zymography are performed essentially as described (Heusen et al., Anal.

Blochem., 102:196-202 (1980); Wilson et al., Journal of Urology, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1/8 SDS gels containing 1% gelain orcasein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis apear as clear areas agains the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

[9069] Processe activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mMNaPO<sub>4</sub>, Inm EDTA, and ImM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260mm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control.

[0070] Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., Methods of Enzymatic Analysis, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward. Apolied Science, 251-317 (1983)).

#### Example 30: Identifying Serine Protease Substrate Specificity

[0971] Methods known in the art or described herein may be used to determine the substrate specificity of the polypeptides of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional seanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

### Example 31: Ligand Binding Assays

[10972] The following assay may be used to assess ligand binding activity of the polypeptides of the invention

Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for a polypeptide is radiolabelled to high specific activity (50-2000 Ct/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards its polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

#### Example 32: Functional Assay in Xenopus Oocytes

10974 | Capped RNA transcripts from linearized plasmid templates encoding the polypeptides of the invention are synthesized in vitro with RNA polymerases in accordance with standard procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/mi. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocyte) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual Xenopus oocytes in response polypeptides and polypeptide agonist exposure. Recordings are made in Ca2+ free Barth's medium at room temperature. The Xenopus system can be used to screen known ligands and tissue/cell extracts for activating ligands.

#### Example 33: Microphysiometric Assays

[0975] Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the activation of polypeptide which is coupled to an energy utilizing intracellular signaling nathway.

### Example 34: Extract/Cell Supernatant Screening

[19976] A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agoniss). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the polypeptides of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is isolated and identified.

## Example 35: Calcium and cAMP Functional Assays

10977] Seven transmembrane receptors which are expressed in HEK 293 cells have been shown to be coupled functionally to activation of Pt.C and calcium mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control cells were observed to be in the normal, 100 nM to 200 nM, range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the

stimulation or inhibition of cAMP production using standard cAMP quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

### Example 36: ATP-binding assav

[0978] The following assay may be used to assess ATP-binding activity of polypeptides of the invention

ATP-binding activity of the polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,888,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenyl-5-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (75 p-ATP) (5 mCt/µmol, ICN, Irvine CA.) is added to a final concentration of 100 µM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 mm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the polypeptides.

#### Example 37: Small Molecule Screening

109801 This invention is particularly useful for screening therapetutic compounds by using the polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes cukaryotic or prokaryotic bost cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and polypeptide of the invention.

[0981] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the invention. These methods comprise contacting such an agent with a polypeptide of the invention or fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the invention.

[1082] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with polypeptides of the invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid sunport.

[10983] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### Example 38: Phosphorylation Assay

10984] In order to assay for phosphorylation activity of the polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled <sup>32</sup>P-ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The polypeptides of the invention are incubated with the protein substrate, <sup>32</sup>P-ATP, and a kinase buffer. The <sup>32</sup>P incorporated into the substrate is then separated from free <sup>32</sup>P-ATP by electrophoresis, and the incorporated <sup>32</sup>P is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the polypeptides of the invention.

Example 39: Detection of Phosphorylation Activity (Activation) of the Polypeptides of the Invention in the Presence of Polypeptide Ligands

[1985] Methods known in the art or described herein may be used to determine the phosphorylation activity of the polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference)

Example 40: Identification Of Signal Transduction Proteins That Interact With Polypeptides
Of The Present Invention

10986] The purified polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled polypeptides of the invention are useful as reagents for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptides of the invention are covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The protein complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

[0987] The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the polypeptides of the invention.

[1988] In order to assay for scrine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the scrinc/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on scrine and threonine residues with cAMP-dependent Protein Kinase in the presence of [\*\*P]ATP. Protein scrine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphata from \$2P\$-labeled MyBP.

#### Example 42; Interaction of Serine/Threonine Phosphatases with other Proteins

10989] The polypeptides of the invention with serine/threonine phosphatase activity as determined in Example 41 are research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, labeled polypeptide(s) of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptide of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The polypeptides of the invention -complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate aDNA library.

## Example 43: Assaying for Heparanase Activity

[0990] In order to assay for heparanase activity of the polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, L, et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells (1 x 10 $^{\circ}$  cells per 35-mm dish) are incubated for 18 hrs a 37 $^{\circ}$ C, pH 6.2-6.6, with  $^{38}$ S-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are clutted from Sepharose 6B at 0.5 ×  $K_{8x} > 0.8$  (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the polypeptides of the invention in cleaving hearan sulfate.

#### Example 44: Immobilization of biomolecules

no991] This example provides a method for the stabilization of polypeptides of the invention in nonhost cell lipid bilayer constucts (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of polypeptides of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular domain of the polypeptides of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of polypeptides of the invention in washed membranes is incubated with 20 mM NaIO4 and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl2, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylelucoside).

#### Example 45: TAOMAN®

Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with DNase I (Life Technologies) to remove any contaminating genomic DNA before reverse transcription.) Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of TAQMAN® Buffer A (Perkin-Elmer, 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM MgCl<sub>3</sub>, 240 µM each dNTP, 0.4 units RNase inhibitor (Promega), 8%glycerol, 0.012% Tween-20, 0.05% gelatin, 0.3uM primers, 0.1uM probe, 0.025units AMPLITAQ GOLD® (Perkin-Elmer) and 2.5 units SUPERSCRIPT™ II reverse transcriptase (Life Technologies). As a control for genomic contamination, parallel reactions are setup without reverse transcriptase. The relative abundance of (unknown) and 188 RNAs are assessed by using the Applied Biosystems Prism 7700 Sequence Detection System (Livak, K. J., Flood, S. J., Marmaro, J., Giusti, W. & Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are carried out at 48°C for 30 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1 min. Reactions are performed in triplicate.

[0993] Primers (f & r) and FRET probes sets are designed using Primer Express Software (Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-Elmer).

## Example 46: Assays for Metalloproteinase Activity

[0994] Metalloproteinases (EC 3.4.24-) are peptide hydrolases which use metal ions, such as Zn<sup>3+</sup>, as the catalytic mechanism. Metalloproteinase activity of polypeptides of the present invention can be assayed according to the following methods.

Proteolysis of alpha-2-macroglobulin

10995] To confirm protease activity, purified polypeptides of the invention are mixed with the substrate alpha-2-macroglobulin (0.2 unit/mt]. Bochringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, 147.5, 0.2 M NaCl, 10 mM CaCl<sub>2</sub>, 25 µM ZnCl<sub>2</sub> and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyaerylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular weight bands as compared to the negative control.

Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases

[6996] Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND HgCl<sub>2</sub>), peptide metalloproteinase inhibitors (TIMF-1 and TIMF-2), and commercial small molecule MMP inhibitors) are used to characterize the proteolytic activity of polypeptides of the invention. The three synthetic MMP inhibitors used are: MMP inhibitors I,  $[IC_{50} = 1.0 \mu M$  against MMP-1 and MMP-8;  $IC_{50} = 30 \mu M$  against MMP-9;  $IC_{50} = 1.0 \mu M$  against MMP-3 (stromelysin-1) inhibitor  $IC_{50} = 5 \mu M$  against MMP-3]; MMP-3 (stromelysin-1) inhibitor  $IC_{50} = 5 \mu M$  against MMP-3).

and MMP-3 inhibitor II [Ki, = 130 nM against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with purified polypeptides of the invention  $(50\mu g/ml)$  in 22.9  $\mu$ 1 of 1x HEPES buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM CaCl<sub>2</sub>, 25  $\mu$ M ZnCl<sub>2</sub> and 0.05%Brij-35) and incubated at room temperature (24 °C) for 2-1r, then 7.1  $\mu$ 1 of substrate alpha-2-macroglobulin (0.2 unit/ml) is added and incubated at 37°C for 20-1r. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

Synthetic Fluorogenic Peptide Substrates Cleavage Assay

[0997] The substrate specificity for polypeptides of the invention with demonstrated metalloproteinase activity can be determined using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor-α (TNF-α) converting enzyme (TACE). All the substrates are prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500 μM. Fluorescent assays are performed by using a Perkin Elmer LS 50B luminescence spectrometer equipped with a constant temperature water bath. The excitation λ is 328 mm and the emission λ is 393 mm. Briefly, the assay is carried out by incubating 176 μ1 Ix HEPES buffer (0.2 M NaCl, 10 mM CaCl<sub>2</sub>, 0.05% Brij-35 and 50 mM HEPES, pH 7.5) with 4 μ1 of substrate solution (50 μM) at 25 °C for 15 minutes, and then adding 20 μ1 of a purified polypeptide of the invention into the assay cuvett. The final concentration of substrate is 1 μM. Initial hydrolysis rates are monitored for 30-min.

# Example 47: Characterization of the cDNA contained in a deposited plasmid

[0998] The size of the cDNA insert contained in a deposited plasmid may be routinely determined using techniques known in the art, such as PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the cDNA sequence. For example, two primers of 17-30 nucleotides derived from each end of the cDNA (i.e., hybridizable to the absolute 5' nucleotide or the 3' nucleotide end of the sequence of SEQ ID NO:X, respectively) are synthesized and used to amplify the cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product. It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

#### Incorporation by Reference

109991 The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. In addition, the sequence listing submitted herewith is incorporated herein by reference in its entirety. The specification and sequence listing of each of the following U.S. and PCT applications are herein incorporated by reference in their entirety: U.S. Appln. No. 60/040,162 filed on 07-Mar-1997, U.S. Appln. No. 60/043,576 filed on 11-Apr-1997, U.S. Appln. No. 60/047,601 filed on 23-May-1997, U.S. Appln. No. 60/056,845 filed on 22-Aug-1997, U.S. Appln, No. 60/043,580 filed on 11-Apr-1997, U.S. Appln, No. 60/047,599 filed on 23-May-1997. U.S. Appln. No. 60/056,664 filed on 22-Aug-1997, U.S. Appln. No. 60/043,314 filed on 11-Apr-1997, U.S. Appln. No. 60/047,632 filed on 23-May-1997, U.S. Appln. No. 60/056,892 filed on 22-Aug-1997, U.S. Appln. No. 60/043,568 filed on 11-Apr-1997, U.S. Appln. No. 60/047,595 filed on 23-May-1997, U.S. Appln. No. 60/056,632 filed on 22-Aug-1997, U.S. Appln. No. 60/043,578 filed on 11-Apr-1997, U.S. Appln. No. 60/040,333 filed on 07-Mar-1997, U.S. Appln. No. 60/043,670 filed on 11-Apr-1997, U.S. Appln. No. 60/047,596 filed on 23-May-1997, U.S. Appln. No. 60/056,864 filed on 22-Aug-1997, U.S. Appln. No. 60/043,674 filed on 11-Apr-1997, U.S. Appln. No. 60/047,612 filed on 23-May-1997, U.S. Appln. No. 60/056,631 filed on 22-Aug-1997, U.S. Appln. No. 60/043,569 filed on 11-Apr-1997, U.S. Appln. No. 60/047,588 filed on 23-May-1997, U.S. Appln. No. 60/056,876 filed on 22-Aug-1997, U.S. Appln. No. 60/043,671 filed on 11-Apr-1997, U.S. Appln. No. 60/043,311 filed on 11-Apr-1997, U.S. Appln, No. 60/038,621 filed on 07-Mar-1997, U.S. Appln, No. 60/043,672 filed on 11-Apr-1997, U.S. Appln. No. 60/047,613 filed on 23-May-1997, U.S. Appln. No. 60/056,636 filed on 22-Aug-1997, U.S. Appln. No. 60/043,669 filed on 11-Apr-1997, U.S. Appln. No. 60/047,582 filed on 23-May-1997, U.S. Appln. No. 60/056,910 filed on 22-Aug-1997, U.S. Appln. No. 60/043,315 filed on 11-Apr-1997, U.S. Appln. No. 60/047,598 filed on 23-May-1997, U.S. Appln. No. 60/056,874 filed on 22-Aug-1997, U.S. Appln. No. 60/043,312 filed on 11-Apr-1997, U.S. Appln. No. 60/047,585 filed on 23-May-1997, U.S. Appln. No. 60/056,881 filed on 22-Aug-1997, U.S. Appln. No. 60/043,313 filed on 11-Apr-1997, U.S. Appln. No. 60/047,586 filed on 23-May-1997, U.S. Appln. No. 60/056,909 filed on 22-Aug-1997, U.S. Appln. No. 60/040,161 filed on 07-Mar-1997, U.S. Appln. No. 60/047,587 filed on 23-May-1997, U.S. Appln. No. 60/056,879 filed on 22-Aug-1997, U.S. Appln. No. 60/047,500 filed on 23-May-1997, U.S. Appln, No. 60/056,880 filed on 22-Aug-1997, U.S. Appln, No. 60/047,584 filed on 23-May-1997, U.S. Appln. No. 60/056,894 filed on 22-Aug-1997, U.S. Appln. No. 60/047,492 filed on 23-May-1997, U.S. Appln. No. 60/056,911 filed on 22-Aug-1997, U.S. Appln. No. 60/040,626 filed on 07-Mar-1997, U.S. Appln. No. 60/047,503 filed on 23-May-1997, U.S. Appln. No. 60/056,903 filed on 22-Aug-1997, U.S. Appln. No. 60/047,501 filed on 23-May-1997, U.S. Appln. No. 60/056,637 filed on 22-Aug-1997, U.S. Appln. No. 60/047,590 filed on 23-May-1997, U.S. Appln. No. 60/056,875 filed on 22-Aug-1997, U.S. Appin, No. 60/047,581 filed on 23-May-1997, U.S. Appin, No. 60/056,882 filed on 22-Aug-1997, U.S. Appin. No. 60/047,592 filed on 23-May-1997, U.S. Appin. No. 60/056,888 filed on 22-Aug-1997, U.S. Appln. No. 60/040,334 filed on 07-Mar-1997, U.S. Appln. No. 60/047,618 filed on 23-May-1997, U.S. Appln. No. 60/056,872 filed on 22-Aug-1997, U.S. Appln. No. 60/047,617 filed on 23-May-1997, U.S.

Appln. No. 60/056,662 filed on 22-Aug-1997, U.S. Appln. No. 60/047,589 filed on 23-May-1997, U.S. Appln. No. 60/056,862 filed on 22-Aug-1997, U.S. Appln. No. 60/047,594 filed on 23-May-1997, U.S. Appln. No. 60/056,884 filed on 22-Aug-1997, U.S. Appln. No. 60/047,583 filed on 23-May-1997, U.S. Appln, No. 60/056,878 filed on 22-Aug-1997, U.S. Appln, No. 60/040,336 filed on 07-Mar-1997, U.S. Appln. No. 60/047,502 filed on 23-May-1997, U.S. Appln. No. 60/056,893 filed on 22-Aug-1997, U.S. Appln. No. 60/047,633 filed on 23-May-1997, U.S. Appln. No. 60/056,630 filed on 22-Aug-1997, U.S. Appln. No. 60/047,593 filed on 23-May-1997, U.S. Appln. No. 60/056,887 filed on 22-Aug-1997, U.S. Appln. No. 60/040,163 filed on 07-Mar-1997, U.S. Appln. No. 60/047,597 filed on 23-May-1997, U.S. Appln, No. 60/056,889 filed on 22-Aug-1997, U.S. Appln, No. 60/047,615 filed on 23-May-1997, U.S. Appln, No. 60/056,877 filed on 22-Aug-1997, U.S. Appln, No. 60/047,600 filed on 23-May-1997, U.S. Appln. No. 60/056,886 filed on 22-Aug-1997, U.S. Appln. No. 60/047,614 filed on 23-May-1997, U.S. Appln. No. 60/056,908 filed on 22-Aug-1997, U.S. Appln. No. 60/040,710 filed on 14-Mar-1997, U.S. Appln. No. 60/050,934 filed on 30-May-1997, U.S. Appln. No. 60/048,100 filed on 30-May-1997, U.S. Appln. No. 60/040,762 filed on 14-Mar-1997, U.S. Appln. No. 60/048,357 filed on 30-May-1997, U.S. Appln. No. 60/048,189 filed on 30-May-1997, U.S. Appln. No. 60/041,277 filed on 21-Mar-1997, U.S. Appln. No. 60/048,188 filed on 30-May-1997, U.S. Appln. No. 60/048,094 filed on 30-May-1997, U.S. Appln. No. 60/048,350 filed on 30-May-1997, U.S. Appln. No. 60/048,135 filed on 30-May-1997, U.S. Appln. No. 60/042,344 filed on 21-Mar-1997, U.S. Appln. No. 60/048,187 filed on 30-May-1997, U.S. Appln. No. 60/048,099 filed on 30-May-1997, U.S. Appln. No. 60/050,937 filed on 30-May-1997, U.S. Appln. No. 60/048,352 filed on 30-May-1997, U.S. Appln. No. 60/041,276 filed on 21-Mar-1997, U.S. Appln. No. 60/048,069 filed on 30-May-1997, U.S. Appln. No. 60/048,131 filed on 30-May-1997, U.S. Appln. No. 60/048,186 filed on 30-May-1997, U.S. Appln. No. 60/048,095 filed on 30-May-1997, U.S. Appln. No. 60/041,281 filed on 21-Mar-1997, U.S. Appln. No. 60/048,355 filed on 30-May-1997, U.S. Appln. No. 60/048,096 filed on 30-May-1997, U.S. Appln. No. 60/048,351 filed on 30-May-1997, U.S. Appln. No. 60/048,154 filed on 30-May-1997, U.S. Appln. No. 60/048,160 filed on 30-May-1997, U.S. Appln. No. 60/042,825 filed on 08-Apr-1997, U.S. Appln. No. 60/048,070 filed on 30-May-1997, U.S. Appln. No. 60/042,727 filed on 08-Apr-1997, U.S. Appln. No. 60/048,068 filed on 30-May-1997, U.S. Appln. No. 60/042,726 filed on 08-Apr-1997, U.S. Appln. No. 60/048,184 filed on 30-May-1997, U.S. Appln. No. 60/042,728 filed on 08-Apr-1997, U.S. Appln. No. 60/042,754 filed on 08-Apr-1997, U.S. Appln. No. 60/048,190 filed on 30-May-1997, U.S. Appln. No. 60/044,039 filed on 30-May-1997, U.S. Appln, No. 60/048,093 filed on 30-May-1997, U.S. Appln, No. 60/048,885 filed on 06-Jun-1997, U.S. Appln. No. 60/057,645 filed on 05-Sep-1997, U.S. Appln. No. 60/049,375 filed on 06-Jun-1997, U.S. Appln. No. 60/057,642 filed on 05-Sep-1997, U.S. Appln. No. 60/048,881 filed on 06-Jun-1997, U.S. Appln. No. 60/057,668 filed on 05-Sep-1997, U.S. Appln. No. 60/048,880 filed on 06-Jun-1997, U.S. Appln. No. 60/057,635 filed on 05-Sep-1997, U.S. Appln. No. 60/048,896 filed on 06-Jun-1997, U.S. Appln. No. 60/057,627 filed on 05-Sep-1997, U.S. Appln, No. 60/049,020 filed on 06-Jun-1997, U.S. Appln, No. 60/057,667 filed on 05-Sep-1997, U.S. Appln. No. 60/048,876 filed on 06-Jun-1997, U.S. Appln. No. 60/057,666 filed on 05-Sep-1997, U.S. Appln. No. 60/048,895 filed on 06-Jun-1997, U.S. Appln. No. 60/057,764 filed on 05-Sep-1997, U.S. Appln. No. 60/048,884 filed on 06-Jun-1997, U.S. Appln. No.

60/057,643 filed on 05-Sep-1997, U.S. Appln. No. 60/048,894 filed on 06-Jun-1997, U.S. Appln. No. 60/057,769 filed on 05-Sep-1997, U.S. Appln. No. 60/048,971 filed on 06-Jun-1997, U.S. Appln. No. 60/057,763 filed on 05-Sep-1997, U.S. Appln. No. 60/048,964 filed on 06-Jun-1997, U.S. Appln. No. 60/057,650 filed on 05-Sep-1997, U.S. Appln. No. 60/048,882 filed on 06-Jun-1997, U.S. Appln. No. 60/057,584 filed on 05-Sep-1997, U.S. Appln. No. 60/048,899 filed on 06-Jun-1997, U.S. Appln. No. 60/057,647 filed on 05-Sep-1997, U.S. Appln. No. 60/048,893 filed on 06-Jun-1997, U.S. Appln. No. 60/057,661 filed on 05-Sep-1997, U.S. Appln. No. 60/048,900 filed on 06-Jun-1997, U.S. Appln. No. 60/057,662 filed on 05-Sep-1997, U.S. Appln. No. 60/048,901 filed on 06-Jun-1997, U.S. Appln. No. 60/057,646 filed on 05-Sep-1997, U.S. Appln, No. 60/048,892 filed on 06-Jun-1997, U.S. Appln, No. 60/057,654 filed on 05-Sep-1997, U.S. Appln, No. 60/048,915 filed on 06-Jun-1997, U.S. Appln, No. 60/057,651 filed on 05-Sep-1997, U.S. Appln. No. 60/049,019 filed on 06-Jun-1997, U.S. Appln. No. 60/057,644 filed on 05-Sep-1997, U.S. Appln. No. 60/048,970 filed on 06-Jun-1997, U.S. Appln. No. 60/057,765 filed on 05-Sep-1997, U.S. Appln. No. 60/048,972 filed on 06-Jun-1997, U.S. Appln. No. 60/057,762 filed on 05-Sep-1997, U.S. Appln. No. 60/048,916 filed on 06-Jun-1997, U.S. Appln. No. 60/057,775 filed on 05-Sep-1997, U.S. Appln. No. 60/049,373 filed on 06-Jun-1997, U.S. Appln. No. 60/057,648 filed on 05-Sep-1997, U.S. Appln. No. 60/048,875 filed on 06-Jun-1997, U.S. Appln. No. 60/057,774 filed on 05-Sep-1997, U.S. Appln. No. 60/049,374 filed on 06-Jun-1997, U.S. Appln. No. 60/057,649 filed on 05-Sep-1997, U.S. Appln. No. 60/048,917 filed on 06-Jun-1997, U.S. Appln. No. 60/057,770 filed on 05-Sep-1997, U.S. Appln, No. 60/048,949 filed on 06-Jun-1997, U.S. Appln, No. 60/057,771 filed on 05-Sep-1997, U.S. Appln. No. 60/048,974 filed on 06-Jun-1997, U.S. Appln. No. 60/057,761 filed on 05-Sep-1997, U.S. Appln. No. 60/048,883 filed on 06-Jun-1997, U.S. Appln. No. 60/057,760 filed on 05-Sep-1997, U.S. Appln. No. 60/048,897 filed on 06-Jun-1997, U.S. Appln. No. 60/057,776 filed on 05-Sep-1997, U.S. Appln. No. 60/048,898 filed on 06-Jun-1997, U.S. Appln. No. 60/057,778 filed on 05-Sep-1997, U.S. Appln. No. 60/048,962 filed on 06-Jun-1997, U.S. Appln. No. 60/057,629 filed on 05-Sep-1997, U.S. Appln. No. 60/048,963 filed on 06-Jun-1997, U.S. Appln. No. 60/057,628 filed on 05-Sep-1997, U.S. Appln. No. 60/048,877 filed on 06-Jun-1997, U.S. Appln. No. 60/057,777 filed on 05-Sep-1997, U.S. Appln. No. 60/048,878 filed on 06-Jun-1997, U.S. Appln. No. 60/057,634 filed on 05-Sep-1997, U.S. Appln. No. 60/049,608 filed on 13-Jun-1997, U.S. Appln. No. 60/058,669 filed on 12-Sep-1997, U.S. Appln. No. 60/049,566 filed on 13-Jun-1997, U.S. Appln. No. 60/058,668 filed on 12-Sep-1997, U.S. Appln, No. 60/052,989 filed on 13-Jun-1997, U.S. Appln, No. 60/058,750 filed on 12-Sep-1997, U.S. Appln. No. 60/049,607 filed on 13-Jun-1997, U.S. Appln. No. 60/058,665 filed on 12-Sep-1997, U.S. Appln. No. 60/049,611 filed on 13-Jun-1997, U.S. Appln. No. 60/058,971 filed on 12-Sep-1997, U.S. Appln. No. 60/050,901 filed on 13-Jun-1997, U.S. Appln. No. 60/058,972 filed on 12-Sep-1997, U.S. Appln. No. 60/049,609 filed on 13-Jun-1997, U.S. Appln. No. 60/058,975 filed on 12-Sep-1997, U.S. Appln, No. 60/048,356 filed on 30-May-1997, U.S. Appln, No. 60/056,296 filed on 29-Aug-1997, U.S. Appln. No. 60/048,101 filed on 30-May-1997, U.S. Appln. No. 60/056,293 filed on 29-Aug-1997, U.S. Appln. No. 60/050,935 filed on 30-May-1997, U.S. Appln. No. 60/056,250 filed on 29-Aug-1997, U.S. Appln. No. 60/049,610 filed on 13-Jun-1997, U.S. Appln. No. 60/061,060 filed on 02-Oct-1997, U.S. Appln. No. 60/049,606 filed on 13-Jun-1997, U.S. Appln. No.

60/060,841 filed on 02-Oct-1997, U.S. Appln. No. 60/049,550 filed on 13-Jun-1997, U.S. Appln. No. 60/060,834 filed on 02-Oct-1997, U.S. Appln. No. 60/049,549 filed on 13-Jun-1997, U.S. Appln. No. 60/060,865 filed on 02-Oct-1997, U.S. Appln. No. 60/049,548 filed on 13-Jun-1997, U.S. Appln. No. 60/060,844 filed on 02-Oct-1997, U.S. Appln. No. 60/049,547 filed on 13-Jun-1997, U.S. Appln. No. 60/061,059 filed on 02-Oct-1997, U.S. Appln. No. 60/051,381 filed on 01-Jul-1997, U.S. Appln. No. 60/058,598 filed on 12-Sep-1997, U.S. Appln. No. 60/051,480 filed on 01-Jul-1997, U.S. Appln. No. 60/058,663 filed on 12-Sep-1997, U.S. Appln. No. 60/051,926 filed on 08-Jul-1997, U.S. Appln. No. 60/058,785 filed on 12-Sep-1997, U.S. Appln. No. 60/052,793 filed on 08-Jul-1997, U.S. Appln. No. 60/058,664 filed on 12-Sep-1997, U.S. Appln, No. 60/051,925 filed on 08-Jul-1997, U.S. Appln, No. 60/058,660 filed on 12-Sep-1997, U.S. Appln, No. 60/051,929 filed on 08-Jul-1997, U.S. Appln, No. 60/058,661 filed on 12-Sep-1997, U.S. Appln. No. 60/052,803 filed on 08-Jul-1997, U.S. Appln. No. 60/055,722 filed on 18-Aug-1997, U.S. Appln. No. 60/052,732 filed on 08-Jul-1997, U.S. Appln. No. 60/055,723 filed on 18-Aug-1997, U.S. Appln. No. 60/051,932 filed on 08-Jul-1997, U.S. Appln. No. 60/055,948 filed on 18-Aug-1997, U.S. Appln, No. 60/051,931 filed on 08-Jul-1997, U.S. Appln, No. 60/055,949 filed on 18-Aug-1997, U.S. Appln. No. 60/051,916 filed on 08-Jul-1997, U.S. Appln. No. 60/055,953 filed on 18-Aug-1997, U.S. Appln. No. 60/051,930 filed on 08-Jul-1997, U.S. Appln. No. 60/055,950 filed on 18-Aug-1997, U.S. Appln. No. 60/051,918 filed on 08-Jul-1997, U.S. Appln. No. 60/055,947 filed on 18-Aug-1997, U.S. Appln. No. 60/051,920 filed on 08-Jul-1997, U.S. Appln. No. 60/055,964 filed on 18-Aug-1997, U.S. Appln. No. 60/052,733 filed on 08-Jul-1997, U.S. Appln. No. 60/056,360 filed on 18-Aug-1997, U.S. Appln. No. 60/052,795 filed on 08-Jul-1997, U.S. Appln. No. 60/055,684 filed on 18-Aug-1997, U.S. Appln. No. 60/051,919 filed on 08-Jul-1997, U.S. Appln. No. 60/055,984 filed on 18-Aug-1997, U.S. Appln. No. 60/051,928 filed on 08-Jul-1997, U.S. Appln. No. 60/055,954 filed on 18-Aug-1997, U.S. Appln. No. 60/052,870 filed on 16-Jul-1997, U.S. Appln. No. 60/055,952 filed on 18-Aug-1997, U.S. Appln. No. 60/052,871 filed on 16-Jul-1997, U.S. Appln. No. 60/055,725 filed on 18-Aug-1997, U.S. Appln, No. 60/052,872 filed on 16-Jul-1997, U.S. Appln, No. 60/056,359 filed on 18-Aug-1997, U.S. Appln. No. 60/052,661 filed on 16-Jul-1997, U.S. Appln. No. 60/055,985 filed on 18-Aug-1997, U.S. Appln. No. 60/052,874 filed on 16-Jul-1997, U.S. Appln. No. 60/055,724 filed on 18-Aug-1997, U.S. Appln. No. 60/052,873 filed on 16-Jul-1997, U.S. Appln. No. 60/055,726 filed on 18-Aug-1997, U.S. Appln. No. 60/052,875 filed on 16-Jul-1997, U.S. Appln. No. 60/056,361 filed on 18-Aug-1997, U.S. Appln, No. 60/053,440 filed on 22-Jul-1997, U.S. Appln, No. 60/055,989 filed on 18-Aug-1997, U.S. Appln. No. 60/053,441 filed on 22-Jul-1997, U.S. Appln. No. 60/055,946 filed on 18-Aug-1997, U.S. Appln. No. 60/053,442 filed on 22-Jul-1997, U.S. Appln. No. 60/055,683 filed on 18-Aug-1997, U.S. Appln. No. 60/054,212 filed on 30-Jul-1997, U.S. Appln. No. 60/055,968 filed on 18-Aug-1997, U.S. Appln. No. 60/054,209 filed on 30-Jul-1997, U.S. Appln. No. 60/055,972 filed on 18-Aug-1997, U.S. Appln, No. 60/054,234 filed on 30-Jul-1997, U.S. Appln, No. 60/055,969 filed on 18-Aug-1997, U.S. Appln. No. 60/055,386 filed on 05-Aug-1997, U.S. Appln. No. 60/055,986 filed on 18-Aug-1997, U.S. Appln. No. 60/054,807 filed on 05-Aug-1997, U.S. Appln. No. 60/055,970 filed on 18-Aug-1997, U.S. Appln. No. 60/054,215 filed on 30-Jul-1997, U.S. Appln. No. 60/056,543 filed on 19-Aug-1997, U.S. Appln. No. 60/054,218 filed on 30-Jul-1997, U.S. Appln. No.

60/056,561 filed on 19-Aug-1997, U.S. Appln. No. 60/054,214 filed on 30-Jul-1997, U.S. Appln. No. 60/056,534 filed on 19-Aug-1997, U.S. Appln. No. 60/054,236 filed on 30-Jul-1997, U.S. Appln. No. 60/056,729 filed on 19-Aug-1997, U.S. Appln. No. 60/054,213 filed on 30-Jul-1997, U.S. Appln. No. 60/056,727 filed on 19-Aug-1997, U.S. Appln, No. 60/054,211 filed on 30-Jul-1997, U.S. Appln, No. 60/056,554 filed on 19-Aug-1997, U.S. Appln. No. 60/054,217 filed on 30-Jul-1997, U.S. Appln. No. 60/056,730 filed on 19-Aug-1997, U.S. Appln. No. 60/055,312 filed on 05-Aug-1997, U.S. Appln. No. 60/056,563 filed on 19-Aug-1997, U.S. Appln. No. 60/055,309 filed on 05-Aug-1997, U.S. Appln. No. 60/056,557 filed on 19-Aug-1997, U.S. Appln. No. 60/055,310 filed on 05-Aug-1997, U.S. Appln. No. 60/056,371 filed on 19-Aug-1997, U.S. Appln, No. 60/054,798 filed on 05-Aug-1997, U.S. Appln, No. 60/056,732 filed on 19-Aug-1997, U.S. Appln, No. 60/056,369 filed on 19-Aug-1997, U.S. Appln, No. 60/056,535 filed on 19-Aug-1997, U.S. Appln. No. 60/056,556 filed on 19-Aug-1997, U.S. Appln. No. 60/056,555 filed on 19-Aug-1997, U.S. Appln. No. 60/054,806 filed on 05-Aug-1997, U.S. Appln. No. 60/056,366 filed on 19-Aug-1997, U.S. Appln. No. 60/054,809 filed on 05-Aug-1997, U.S. Appln. No. 60/056,364 filed on 19-Aug-1997, U.S. Appln. No. 60/054,804 filed on 05-Aug-1997, U.S. Appln. No. 60/056,370 filed on 19-Aug-1997, U.S. Appln. No. 60/054,803 filed on 05-Aug-1997, U.S. Appln. No. 60/056,731 filed on 19-Aug-1997, U.S. Appln. No. 60/055,311 filed on 05-Aug-1997, U.S. Appln. No. 60/056,365 filed on 19-Aug-1997, U.S. Appln. No. 60/054,808 filed on 05-Aug-1997, U.S. Appln. No. 60/056,367 filed on 19-Aug-1997, U.S. Appln. No. 60/056,726 filed on 19-Aug-1997, U.S. Appln. No. 60/056,368 filed on 19-Aug-1997, U.S. Appln. No. 60/056,728 filed on 19-Aug-1997, U.S. Appln. No. 60/056,628 filed on 19-Aug-1997, U.S. Appln. No. 60/056,629 filed on 19-Aug-1997, U.S. Appln. No. 60/056,270 filed on 29-Aug-1997, U.S. Appln. No. 60/056,271 filed on 29-Aug-1997, U.S. Appln. No. 60/056,247 filed on 29-Aug-1997, U.S. Appln. No. 60/056,073 filed on 29-Aug-1997, U.S. Appln. No. 60/057,669 filed on 05-Sep-1997, U.S. Appln. No. 60/057,663 filed on 05-Sep-1997, U.S. Appln. No. 60/057,626 filed on 05-Sep-1997, U.S. Appln. No. 60/058,666 filed on 12-Sep-1997, U.S. Appln. No. 60/058.973 filed on 12-Sep-1997, U.S. Appln. No. 60/058.974 filed on 12-Sep-1997, U.S. Appln. No. 60/058,667 filed on 12-Sep-1997, U.S. Appln. No. 60/060,837 filed on 02-Oct-1997, U.S. Appln. No. 60/060,862 filed on 02-Oct-1997, U.S. Appln. No. 60/060,839 filed on 02-Oct-1997, U.S. Appln. No. 60/060,866 filed on 02-Oct-1997, U.S. Appln. No. 60/060,843 filed on 02-Oct-1997, U.S. Appln. No. 60/060,836 filed on 02-Oct-1997, U.S. Appln. No. 60/060,838 filed on 02-Oct-1997, U.S. Appln. No. 60/060,874 filed on 02-Oct-1997, U.S. Appln, No. 60/060,833 filed on 02-Oct-1997, U.S. Appln, No. 60/060,884 filed on 02-Oct-1997, U.S. Appln. No. 60/060,880 filed on 02-Oct-1997, U.S. Appln. No. 60/061,463 filed on 09-Oct-1997, U.S. Appln. No. 60/061,529 filed on 09-Oct-1997, U.S. Appln. No. 60/071,498 filed on 09-Oct-1997, U.S. Appln. No. 60/061,527 filed on 09-Oct-1997, U.S. Appln. No. 60/061,536 filed on 09-Oct-1997, U.S. Appln. No. 60/061,532 filed on 09-Oct-1997, U.S. Appln. No. 60/063.099 filed on 24-Oct-1997, U.S. Appln, No. 60/063.088 filed on 24-Oct-1997, U.S. Appln, No. 60/063,100 filed on 24-Oct-1997, U.S. Appln. No. 60/063,387 filed on 24-Oct-1997, U.S. Appln. No. 60/063,148 filed on 24-Oct-1997, U.S. Appln. No. 60/063,386 filed on 24-Oct-1997, U.S. Appln. No. 60/062,784 filed on 24-Oct-1997, U.S. Appln. No. 60/063,091 filed on 24-Oct-1997, U.S. Appln. No. 60/063,090 filed on 24-Oct-1997, U.S. Appln. No. 60/063,089 filed on 24-Oct-1997, U.S. Appln. No.

60/063,092 filed on 24-Oct-1997, U.S. Appln. No. 60/063,111 filed on 24-Oct-1997, U.S. Appln. No. 60/063,101 filed on 24-Oct-1997, U.S. Appln. No. 60/063,109 filed on 24-Oct-1997, U.S. Appln. No. 60/063,110 filed on 24-Oct-1997, U.S. Appln. No. 60/063,098 filed on 24-Oct-1997, U.S. Appln. No. 60/063,097 filed on 24-Oct-1997, U.S. Appln, No. 60/064,911 filed on 07-Nov-1997, U.S. Appln, No. 60/064,912 filed on 07-Nov-1997, U.S. Appln. No. 60/064,983 filed on 07-Nov-1997, U.S. Appln. No. 60/064,900 filed on 07-Nov-1997, U.S. Appln. No. 60/064,988 filed on 07-Nov-1997, U.S. Appln. No. 60/064,987 filed on 07-Nov-1997, U.S. Appln. No. 60/064,908 filed on 07-Nov-1997, U.S. Appln. No. 60/064,984 filed on 07-Nov-1997, U.S. Appln. No. 60/064,985 filed on 07-Nov-1997, U.S. Appln. No. 60/066,094 filed on 17-Nov-1997, U.S. Appln, No. 60/066,100 filed on 17-Nov-1997, U.S. Appln, No. 60/066,089 filed on 17-Nov-1997, U.S. Appln, No. 60/066,095 filed on 17-Nov-1997, U.S. Appln, No. 60/066,090 filed on 17-Nov-1997, U.S. Appln. No. 60/068,006 filed on 18-Dec-1997, U.S. Appln. No. 60/068,057 filed on 18-Dec-1997, U.S. Appln. No. 60/068,007 filed on 18-Dec-1997, U.S. Appln. No. 60/068,008 filed on 18-Dec-1997, U.S. Appln. No. 60/068,054 filed on 18-Dec-1997, U.S. Appln. No. 60/068,064 filed on 18-Dec-1997, U.S. Appln. No. 60/068,053 filed on 18-Dec-1997, U.S. Appln. No. 60/070,923 filed on 18-Dec-1997, U.S. Appln. No. 60/068,365 filed on 19-Dec-1997, U.S. Appln. No. 60/068,169 filed on 19-Dec-1997, U.S. Appln. No. 60/068,367 filed on 19-Dec-1997, U.S. Appln. No. 60/068,369 filed on 19-Dec-1997, U.S. Appln. No. 60/068,368 filed on 19-Dec-1997, U.S. Appln. No. 60/070,657 filed on 07-Jan-1998, U.S. Appln. No. 60/070,692 filed on 07-Jan-1998, U.S. Appln. No. 60/070,704 filed on 07-Jan-1998, U.S. Appln. No. 60/070,658 filed on 07-Jan-1998, U.S. Appln. No. 60/073,160 filed on 30-Jan-1998, U.S. Appln, No. 60/073,159 filed on 30-Jan-1998, U.S. Appln, No. 60/073,165 filed on 30-Jan-1998, U.S. Appln, No. 60/073,164 filed on 30-Jan-1998, U.S. Appln, No. 60/073,167 filed on 30-Jan-1998, U.S. Appln. No. 60/073,162 filed on 30-Jan-1998, U.S. Appln. No. 60/073,161 filed on 30-Jan-1998, U.S. Appln. No. 60/073,170 filed on 30-Jan-1998, U.S. Appln. No. 60/074,141 filed on 09-Feb-1998, U.S. Appln. No. 60/074,341 filed on 09-Feb-1998, U.S. Appln. No. 60/074,037 filed on 09-Feb-1998, U.S. Appln. No. 60/074,157 filed on 09-Feb-1998, U.S. Appln. No. 60/074,118 filed on 09-Feb-1998, U.S. Appln. No. 60/076,051 filed on 26-Feb-1998, U.S. Appln. No. 60/076,053 filed on 26-Feb-1998, U.S. Appln. No. 60/076,054 filed on 26-Feb-1998, U.S. Appln. No. 60/076,052 filed on 26-Feb-1998, U.S. Appln. No. 60/076,057 filed on 26-Feb-1998, U.S. Appln. No. 60/077,714 filed on 12-Mar-1998, U.S. Appln. No. 60/077,687 filed on 12-Mar-1998, U.S. Appln. No. 60/077,686 filed on 12-Mar-1998, U.S. Appln, No. 60/077,696 filed on 12-Mar-1998, U.S. Appln, No. 60/078,566 filed on 19-Mar-1998, U.S. Appln, No. 60/078,574 filed on 19-Mar-1998, U.S. Appln, No. 60/078,576 filed on 19-Mar-1998, U.S. Appln. No. 60/078,579 filed on 19-Mar-1998, U.S. Appln. No. 60/078,563 filed on 19-Mar-1998, U.S. Appln. No. 60/078,573 filed on 19-Mar-1998, U.S. Appln. No. 60/078,578 filed on 19-Mar-1998, U.S. Appln. No. 60/078,581 filed on 19-Mar-1998, U.S. Appln. No. 60/078,577 filed on 19-Mar-1998, U.S. Appln. No. 60/080,314 filed on 01-Apr-1998, U.S. Appln. No. 60/080,312 filed on 01-Apr-1998, U.S. Appln, No. 60/080,313 filed on 01-Apr-1998, U.S. Appln, No. 60/085,180 filed on 12-May-1998, U.S. Appln. No. 60/085,105 filed on 12-May-1998, U.S. Appln. No. 60/085,094 filed on 12-May-1998, U.S. Appln. No. 60/085,093 filed on 12-May-1998, U.S. Appln. No. 60/085,924 filed on 18-May-1998, U.S. Appln. No. 60/085,906 filed on 18-May-1998, U.S. Appln. No. 60/085,927 filed on 18-May-1998, U.S. Appln. No. 60/085,920 filed on 18-May-1998, U.S. Appln. No. 60/085,928 filed on 18-May-1998, U.S. Appln. No. 60/085,925 filed on 18-May-1998, U.S. Appln. No. 60/085,921 filed on 18-May-1998, U.S. Appln. No. 60/085,923 filed on 18-May-1998, U.S. Appln. No. 60/085,922 filed on 18-May-1998, U.S. Appln, No. 60/090,112 filed on 22-Jun-1998, U.S. Appln, No. 60/089,508 filed on 16-Jun-1998, U.S. Appln. No. 60/089,507 filed on 16-Jun-1998, U.S. Appln. No. 60/089,510 filed on 16-Jun-1998, U.S. Appln. No. 60/089,509 filed on 16-Jun-1998, U.S. Appln. No. 60/090,113 filed on 22-Jun-1998, U.S. Appln. No. 60/092,956 filed on 15-Jul-1998, U.S. Appln. No. 60/092,921 filed on 15-Jul-1998, U.S. Appln. No. 60/092,922 filed on 15-Jul-1998, U.S. Appln. No. 60/094,657 filed on 30-Jul-1998, U.S. Appln, No. 60/095,486 filed on 05-Aug-1998, U.S. Appln, No. 60/096,319 filed on 12-Aug-1998, U.S. Appln, No. 60/095,455 filed on 06-Aug-1998, U.S. Appln, No. 60/095,454 filed on 06-Aug-1998, U.S. Appln. No. 60/097,917 filed on 25-Aug-1998, U.S. Appln. No. 60/098,634 filed on 31-Aug-1998, U.S. Appln. No. 60/101,546 filed on 23-Sep-1998, U.S. Appln. No. 60/102,895 filed on 02-Oct-1998, U.S. Appln. No. 60/108,207 filed on 12-Nov-1998, U.S. Appln. No. 60/113,006 filed on 18-Dec-1998, U.S. Appln. No. 60/112,809 filed on 17-Dec-1998, U.S. Appln. No. 60/116,330 filed on 19-Jan-1999, U.S. Appln. No. 60/119,468 filed on 10-Feb-1999, U.S. Appln. No. 60/125,055 filed on 18-Mar-1999, U.S. Appln. No. 60/128,693 filed on 09-Apr-1999, U.S. Appln. No. 60/130,991 filed on 26-Apr-1999, U.S. Appln. No. 60/137,725 filed on 07-Jun-1999, U.S. Appln. No. 60/145,220 filed on 23-Jul-1999, U.S. Appln. No. 60/149,182 filed on 17-Aug-1999, U.S. Appln. No. 60/152,317 filed on 03-Sep-1999, U.S. Appln, No. 60/152,315 filed on 03-Sep-1999, U.S. Appln, No. 60/155,709 filed on 24-Sep-1999, U.S. Appln. No. 60/163,085 filed on 02-Nov-1999, U.S. Appln. No. 60/172,411 filed on 17-Dec-1999, U.S. Appln. No. 60/162,239 filed on 29-Oct-1999, U.S. Appln. No. 60/215,139 filed on 30-Jun-2000, U.S. Appln. No. 60/162,211 filed on 29-Oct-1999, U.S. Appln. No. 60/215,138 filed on 30-Jun-2000, U.S. Appln. No. 60/162,240 filed on 29-Oct-1999, U.S. Appln. No. 60/215,131 filed on 30-Jun-2000, U.S. Appln. No. 60/162,237 filed on 29-Oct-1999, U.S. Appln. No. 60/219,666 filed on 21-Jul-2000, U.S. Appln. No. 60/162,238 filed on 29-Oct-1999, U.S. Appln. No. 60/215,134 filed on 30-Jun-2000, U.S. Appln. No. 60/163,580 filed on 05-Nov-1999, U.S. Appln. No. 60/215,130 filed on 30-Jun-2000, U.S. Appln. No. 60/163,577 filed on 05-Nov-1999, U.S. Appln. No. 60/215,137 filed on 30-Jun-2000, U.S. Appln. No. 60/163,581 filed on 05-Nov-1999, U.S. Appln. No. 60/215,133 filed on 30-Jun-2000, U.S. Appln. No. 60/163,576 filed on 05-Nov-1999, U.S. Appln. No. 60/221,366 filed on 27-Jul-2000, U.S. Appln, No. 60/164,344 filed on 09-Nov-1999, U.S. Appln, No. 60/195,296 filed on 07-Apr-2000, U.S. Appln. No. 60/221,367 filed on 27-Jul-2000, U.S. Appln. No. 60/164,835 filed on 12-Nov-1999, U.S. Appln. No. 60/221,142 filed on 27-Jul-2000, U.S. Appln. No. 60/164,744 filed on 12-Nov-1999, U.S. Appln. No. 60/215,140 filed on 30-Jun-2000, U.S. Appln. No. 60/164,735 filed on 12-Nov-1999, U.S. Appln. No. 60/221,193 filed on 27-Jul-2000, U.S. Appln. No. 60/164,825 filed on 12-Nov-1999, U.S. Appln. No. 60/222,904 filed on 03-Aug-2000, U.S. Appln. No. 60/164,834 filed on 12-Nov-1999, U.S. Appln. No. 60/224,007 filed on 04-Aug-2000, U.S. Appln. No. 60/164,750 filed on 12-Nov-1999, U.S. Appln. No. 60/215,128 filed on 30-Jun-2000, U.S. Appln. No. 60/166,415 filed on 19-Nov-1999, U.S. Appln. No. 60/215,136 filed on 30-Jun-2000, U.S. Appln. No. 60/166,414 filed on 19-Nov-1999, U.S. Appln. No. 60/219,665 filed on 21-Jul-2000, U.S. Appln. No.

60/164,731 filed on 12-Nov-1999, U.S. Appln. No. 60/215,132 filed on 30-Jun-2000, U.S. Appln. No. 60/226,280 filed on 18-Aug-2000, U.S. Appln. No. 60/256,968 filed on 21-Dec-2000, U.S. Appln. No. 60/226,380 filed on 18-Aug-2000, U.S. Appln. No. 60/259,803 filed on 05-Jan-2001, U.S. Appln. No. 60/228,084 filed on 28-Aug-2000, U.S. Appln, No. 09/915,582 filed on 27-Jul-2001, U.S. Appln, No. 60/231,968 filed on 12-Sep-2000, U.S. Appln. No. 60/236,326 filed on 29-Sep-2000, U.S. Appln. No. 60/234,211 filed on 20-Sep-2000, U.S. Appln. No. 60/226,282 filed on 18-Aug-2000, U.S. Appln. No. 60/232,104 filed on 12-Sep-2000, U.S. Appln. No. 60/234,210 filed on 20-Sep-2000, U.S. Appln. No. 60/226,278 filed on 18-Aug-2000, U.S. Appln. No. 60/259,805 filed on 05-Jan-2001, U.S. Appln. No. 60/226,279 filed on 18-Aug-2000, U.S. Appln, No. 60/259,678 filed on 05-Jan-2001, U.S. Appln, No. 60/226,281 filed on 18-Aug-2000, U.S. Appln. No. 60/231,969 filed on 12-Sep-2000, U.S. Appln. No. 60/228,086 filed on 28-Aug-2000, U.S. Appln. No. 60/259,516 filed on 04-Jan-2001, U.S. Appln. No. 60/228,083 filed on 28-Aug-2000, U.S. Appln. No. 60/259,804 filed on 05-Jan-2001, U.S. Appln. No. 60/270,658 filed on 23-Feb-2001, U.S. Appln. No. 60/304,444 filed on 12-Jul-2001, U.S. Appln. No. 60/270,625 filed on 23-Feb-2001, U.S. Appln. No. 60/304,417 filed on 12-Jul-2001, U.S. Appln. No. 60/295,869 filed on 06-Jun-2001, U.S. Appln. No. 60/304,121 filed on 11-Jul-2001, U.S. Appln. No. 60/311,085 filed on 10-Aug-2001, U.S. Appln. No. 60/325,209 filed on 28-Sep-2001, U.S. Appln. No. 60/330,629 filed on 26-Oct-2001, U.S. Appln. No. 60/331,046 filed on 07-Nov-2001, U.S. Appln. No. 60/358,554 filed on 22-Feb-2002, U.S. Appln. No. 60/358,714 filed on 25-Feb-2002, U.S. Appln. No. 60/277,340 filed on 21-Mar-2001, U.S. Appln. No. 60/306,171 filed on 19-Jul-2001, U.S. Appln. No. 60/278.650 filed on 27-Mar-2001, U.S. Appln. No. 60/331,287 filed on 13-Nov-2001, U.S. Appln. No. 09/950,082 filed on 12-Sep-2001, U.S. Appln. No. 09/950,083 filed on 12-Sep-2001, PCT Appln. No. US00/29363 filed on 25-Oct-2000, PCT Appln. No. US00/29360 filed on 25-Oct-2000, PCT Appln. No. US00/29362 filed on 25-Oct-2000, PCT Appln. No. US00/29365 filed on 25-Oct-2000, PCT Appln. No. US00/29364 filed on 25-Oct-2000, PCT Appln. No. US00/30040 filed on 01-Nov-2000, PCT Appln. No. US00/30037 filed on 01-Nov-2000, PCT Appln. No. US00/30045 filed on 01-Nov-2000, PCT Appln. No. US00/30036 filed on 01-Nov-2000, PCT Appln. No. US00/30039 filed on 01-Nov-2000, PCT Appln. No. US00/30654 filed on 08-Nov-2000, PCT Appln. No. US00/30628 filed on 08-Nov-2000, PCT Appln. No. US00/30653 filed on 08-Nov-2000, PCT Appln. No. US00/30629 filed on 08-Nov-2000, PCT Appln. No. US00/30679 filed on 08-Nov-2000, PCT Appln. No. US00/30674 filed on 08-Nov-2000, PCT Appln. No. US00/31162 filed on 15-Nov-2000, PCT Appln, No. US00/31282 filed on 15-Nov-2000, PCT Appln, No. US00/30657 filed on 08-Nov-2000, PCT Appln, No. US01/01396 filed on 17-Jan-2001, PCT Appln, No. US01/01387 filed on 17-Jan-2001, PCT Appln. No. US01/01567 filed on 17-Jan-2001, PCT Appln. No. US01/01431 filed on 17-Jan-2001, PCT Appln. No. US01/01432 filed on 17-Jan-2001, PCT Appln. No. US01/00544 filed on 09-Jan-2001, PCT Appln. No. US01/01435 filed on 17-Jan-2001, PCT Appln. No. US01/01386 filed on 17-Jan-2001, PCT Appln. No. US01/01565 filed on 17-Jan-2001, PCT Appln. No. US01/01394 filed on 17-Jan-2001, PCT Appln, No. US01/01434 filed on 17-Jan-2001, PCT Appln, No. US01/01397 filed on 17-Jan-2001, PCT Appln. No. US01/01385 filed on 17-Jan-2001, PCT Appln. No. US01/01384 filed on 17-Jan-2001, PCT Appln. No. US01/01383 filed on 17-Jan-2001, PCT Appln. No. (Atty. Dkt. No. PS735; unassigned) filed on 21-Feb-2002, PCT Appln. No. (Atty. Dkt. No. PS736;

unassigned) filed on 21-Feb-2002, U.S. Appln. No. 09/148,545 filed on 04-Sep-1998, U.S. Appln. No. 09/621,011 filed on 20-Jul-2000, U.S. Appln. No. 09/981,876 filed on 19-Oct-2001, U.S. Appln. No. 09/149,476 filed on 08-Sep-1998, U.S. Appln. No. 09/809,391 filed on 16-Mar-2001, U.S. Appln. No. 09/882,171 filed on 18-Jun-2001, U.S. Appln, No. 60/190,068 filed on 17-Mar-2000, U.S. Appln, No. 09/152,060 filed on 11-Sep-1998, U.S. Appln. No. 09/852,797 filed on 11-May-2001, U.S. Appln. No. 09/853,161 filed on 11-May-2001, U.S. Appln. No. 09/852,659 filed on 11-May-2001, U.S. Appln. No. 10/058,993 filed on 30-Jan-2002, U.S. Appln. No. 60/265,583 filed on 02-Feb-2001, U.S. Appln. No. 09/154,707 filed on 17-Sep-1998, U.S. Appln. No. 09/966,262 filed on 01-Oct-2001, U.S. Appln. No. 09/983,966 filed on 26-Oct-2001, U.S. Appln. No. 10/059,395 filed on 31-Jan-2002, U.S. Appln. No. 09/984,245 filed on 29-Oct-2001, U.S. Appln, No. 09/166,780 filed on 06-Oct-1998, U.S. Appln, No. 09/577,145 filed on 24-May-2000, U.S. Appln. No. 09/814,122 filed on 22-Mar-2001, U.S. Appln. No. 09/189,144 filed on 10-Nov-1998, U.S. Appln. No. 09/690,454 filed on 18-Oct-2000, U.S. Appln. No. (Atty. Dkt. No. PZ006G13A; unassigned) filed on 05-Feb-2002, U.S. Appln. No. 10/062,599 filed on 05-Feb-2002, U.S. Appln. No. 09/205,258 filed on 04-Dec-1998, U.S. Appln. No. 09/933,767 filed on 22-Aug-2001, U.S. Appln. No. 60/184,836 filed on 24-Feb-2000, U.S. Appln. No. 60/193,170 filed on 29-Mar-2000, U.S. Appln. No. 10/023,282 filed on 20-Dec-2001, U.S. Appln. No. 10/004,860 filed on 07-Dec-2001, U.S. Appln. No. 09/209,462 filed on 11-Dec-1998, U.S. Appln. No. 09/213,365 filed on 17-Dec-1998, U.S. Appln. No. 09/627,081 filed on 27-Jul-2000, U.S. Appln. No. 09/227,357 filed on 08-Jan-1999, U.S. Appln. No. 09/983,802 filed on 25-Oct-2001, U.S. Appln. No. 09/973,278 filed on 10-Oct-2001, U.S. Appln. No. 60/239,899 filed on 13-Oct-2000, U.S. Appln. No. 09/984,490 filed on 30-Oct-2001, U.S. Appln. No. 09/776,724 filed on 06-Feb-2001, U.S. Appln. No. 09/229,982 filed on 14-Jan-1999, U.S. Appln. No. 09/669,688 filed on 26-Sep-2000, U.S. Appln. No. 60/180,909 filed on 08-Feb-2000, U.S. Appln. No. 09/236,557 filed on 26-Jan-1999, U.S. Appln. No. 09/666,984 filed on 21-Sep-2000, U.S. Appln. No. 09/820,649 filed on 30-Mar-2001, U.S. Appln. No. 60/295,558 filed on 05-Jun-2001, U.S. Appln. No. 09/244,112 filed on 04-Feb-1999, U.S. Appln. No. 09/774,639 filed on 01-Feb-2001, U.S. Appln. No. 09/969,730 filed on 04-Oct-2001, U.S. Appln. No. 60/238,291 filed on 06-Oct-2000, U.S. Appln. No. 09/251,329 filed on 17-Feb-1999, U.S. Appln. No. 09/716,128 filed on 17-Nov-2000, U.S. Appln. No. 09/257,179 filed on 25-Feb-1999, U.S. Appln. No. 09/729,835 filed on 06-Dec-2000, U.S. Appln. No. 09/262,109 filed on 04-Mar-1999, U.S. Appln. No. 09/722,329 filed on 28-Nov-2000, U.S. Appln. No. (Atty. Dkt. No. PZ016P1C1; unassigned) filed on 17-Jan-2002, U.S. Appln. No. 60/262,066 filed on 18-Jan-2001, U.S. Appln, No. 09/281,976 filed on 31-Mar-1999, U.S. Appln, No. 09/288,143 filed on 08-Apr-1999. U.S. Appln. No. 09/984,429 filed on 30-Oct-2001, U.S. Appln. No. 60/244,591 filed on 01-Nov-2000, U.S. Appln. No. 09/296,622 filed on 23-Apr-1999, U.S. Appln. No. 09/305,736 filed on 05-May-1999, U.S. Appln. No. 09/818,683 filed on 28-Mar-2001, U.S. Appln. No. 09/974,879 filed on 12-Oct-2001, U.S. Appln. No. 60/239.893 filed on 13-Oct-2000, U.S. Appln. No. 09/334.595 filed on 17-Jun-1999, U.S. Appln. No. 09/348,457 filed on 07-Jul-1999, U.S. Appln, No. 09/739,907 filed on 20-Dec-2000, U.S. Appln, No. 09/938,671 filed on 27-Aug-2001, U.S. Appln. No. 09/363,044 filed on 29-Jul-1999, U.S. Appln. No. 09/813,153 filed on 21-Mar-2001, U.S. Appln. No. 09/949,925 filed on 12-Sep-2001, U.S. Appln. No. 60/232,150 filed on 12-Sep-2000, U.S. Appln. No. 09/369,247 filed on 05-Aug-1999, U.S. Appln. No.

10/062,548 filed on 05-Feb-2002, U.S. Appln. No. 09/382,572 filed on 25-Aug-1999, U.S. Appln. No. 09/716,129 filed on 17-Nov-2000, U.S. Appln. No. 09/393,022 filed on 09-Sep-1999, U.S. Appln. No. 09/798,889 filed on 06-Mar-2001, U.S. Appln. No. 09/397,945 filed on 17-Sep-1999, U.S. Appln. No. 09/437,658 filed on 10-Nov-1999, U.S. Appln, No. 09/892,877 filed on 28-Jun-2001, U.S. Appln, No. 09/948,783 filed on 10-Sep-2001, U.S. Appln. No. 60/231,846 filed on 11-Sep-2000, U.S. Appln. No. 09/461,325 filed on 14-Dec-1999, U.S. Appln. No. 10/050,873 filed on 18-Jan-2002, U.S. Appln. No. 60/263,230 filed on 23-Jan-2001, U.S. Appln. No. 60/263,681 filed on 24-Jan-2001, U.S. Appln. No. 10/012,542 filed on 12-Dec-2001, U.S. Appln. No. 09/482,273 filed on 13-Jan-2000, U.S. Appln. No. 60/234,925 filed on 25-Sep-2000, U.S. Appln, No. 09/984,276 filed on 29-Oct-2001, U.S. Appln, No. 09/984,271 filed on 29-Oct-2001, U.S. Appln, No. 09/489,847 filed on 24-Jan-2000, U.S. Appln, No. 60/350,898 filed on 25-Jan-2002, U.S. Appln. No. 09/511,554 filed on 23-Feb-2000, U.S. Appln. No. 09/739,254 filed on 19-Dec-2000, U.S. Appln. No. 09/904,615 filed on 16-Jul-2001, U.S. Appln. No. 10/054,988 filed on 25-Jan-2002, U.S. Appln. No. 09/531,119 filed on 20-Mar-2000, U.S. Appln. No. 09/820.893 filed on 30-Mar-2001, U.S. Appln, No. 09/565,391 filed on 05-May-2000, U.S. Appln, No. 09/948,820 filed on 10-Sep-2001, U.S. Appln. No. 09/591,316 filed on 09-Jun-2000, U.S. Appln. No. 09/895,298 filed on 02-Jul-2001, U.S. Appln. No. 09/618,150 filed on 17-Jul-2000, U.S. Appln. No. 09/985,153 filed on 01-Nov-2001, U.S. Appln. No. 09/628,508 filed on 28-Jul-2000, U.S. Appln. No. 09/997,131 filed on 30-Nov-2001, U.S. Appln. No. 09/661,453 filed on 13-Sep-2000, U.S. Appln. No. 10/050,882 filed on 18-Jan-2002, U.S. Appln. No. 09/684,524 filed on 10-Oct-2000, U.S. Appln. No. 10/050,704 filed on 18-Jan-2002, U.S. Appln. No. 09/726,643 filed on 01-Dec-2000, U.S. Appln. No. 10/042,141 filed on 11-Jan-2002, U.S. Appln, No. 09/756,168 filed on 09-Jan-2001, U.S. Appln, No. 09/781,417 filed on 13-Feb-2001, U.S. Appln. No. (Atty. Dkt. No. PZ042P1C1; unassigned) filed on 01-Feb-2002, U.S. Appln. No. 09/789,561 filed on 22-Feb-2001, U.S. Appln. No. 09/800,729 filed on 08-Mar-2001, U.S. Appln. No. 09/832,129 filed on 11-Apr-2001, PCT Appln. No. US98/04482 filed on 06-Mar-1998, PCT Appln. No.US98/04493 filed on 06-Mar-1998, PCT Appln. No.US98/04858 filed on 12-Mar-1998, PCT Appln. No.US98/05311 filed on 19-Mar-1998, PCT Appln. No.US98/06801 filed on 07-Apr-1998, PCT Appln. No.US98/10868 filed on 28-May-1998, PCT Appln. No.US98/11422 filed on 04-Jun-1998, PCT Appln. No.US01/05614 filed on 21-Feb-2001, PCT Appln. No.US98/12125 filed on 11-Jun-1998, PCT Appln. No.US98/13608 filed on 30-Jun-1998, PCT Appln. No.US98/13684 filed on 07-Jul-1998, PCT Appln, No. US98/14613 filed on 15-Jul-1998, PCT Appln, No. US98/15949 filed on 29-Jul-1998, PCT Appln. No.US98/16235 filed on 04-Aug-1998, PCT Appln. No.US98/17044 filed on 18-Aug-1998, PCT Appln. No.US98/17709 filed on 27-Aug-1998, PCT Appln. No.US98/18360 filed on 03-Sep-1998, PCT Appln. No.(Atty. Dkt. No. PZ016PCT2; unassigned) filed on 17-Jan-2002, PCT Appln. No.US98/20775 filed on 01-Oct-1998, PCT Appln. No.US98/21142 filed on 08-Oct-1998, PCT Appln. No.US98/22376 filed on 23-Oct-1998, PCT Appln, No.US98/23435 filed on 04-Nov-1998, PCT Appln, No.US98/27059 filed on 17-Dec-1998, PCT Appln. No.US99/00108 filed on 06-Jan-1999, PCT Appln. No.US99/01621 filed on 27-Jan-1999, PCT Appln. No.US99/02293 filed on 04-Feb-1999, PCT Appln. No.US99/03939 filed on 24-Feb-1999, PCT Appln. No.US99/05721 filed on 11-Mar-1999, PCT Appln. No.US99/05804 filed on 18-Mar-1999, PCT Appln. No.US99/09847 filed on 06-May-1999, PCT Appln. No.US99/13418 filed on 15-Jun1999, PCT Appln. No.US99/15849 filed on 14-Jul-1999, PCT Appln. No.US01/00911 filed on 12-Jan-2001, PCT Appln. No.US01/29871 filed on 24-Sep-2001, PCT Appln. No.US99/17130 filed on 29-Jul-1999, PCT Appln. No.US99/19330 filed on 24-Aug-1999, PCT Appln. No.US99/22012 filed on 22-Sep-1999, PCT Appln. No.US99/26409 filed on 09-Nov-1999, PCT Appln. No.US99/29950 filed on 16-Dec-1999, PCT Appln. No.US00/00903 filed on 18-Jan-2000, PCT Appln. No.US00/03062 filed on 08-Feb-2000, PCT Appln. No.US00/06783 filed on 16-Mar-2000, PCT Appln. No.US00/08979 filed on 06-Apr-2000, PCT Appln. No.US00/15187 filed on 02-Jun-2000, PCT Appln. No.US00/19735 filed on 20-Jul-2000, PCT Appln. No.US00/22325 filed on 16-Aug-2000, PCT Appln. No.US00/24008 filed on 31-Aug-2000, PCT Appln. No.US00/26013 filed on 22-Sep-2000, PCT Appln. No.US00/28664 filed on 17-Oct-2000, US Appln. No. 09/833,245 filed on 12-Apr-2001, and PCT Appln. No. US01/11988 filed on 12-Apr-2001, and PCT Appln. No. US02/08124 filed on 19-Mar-2002.